UNIVERSITY OF WASHINGTON
STD Prevention Training Center

STDs—Revenge of the Syph

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Slides courtesy: Matt Golden, Julie Dombrowski, Sue Szabo, Sheila Lukehart

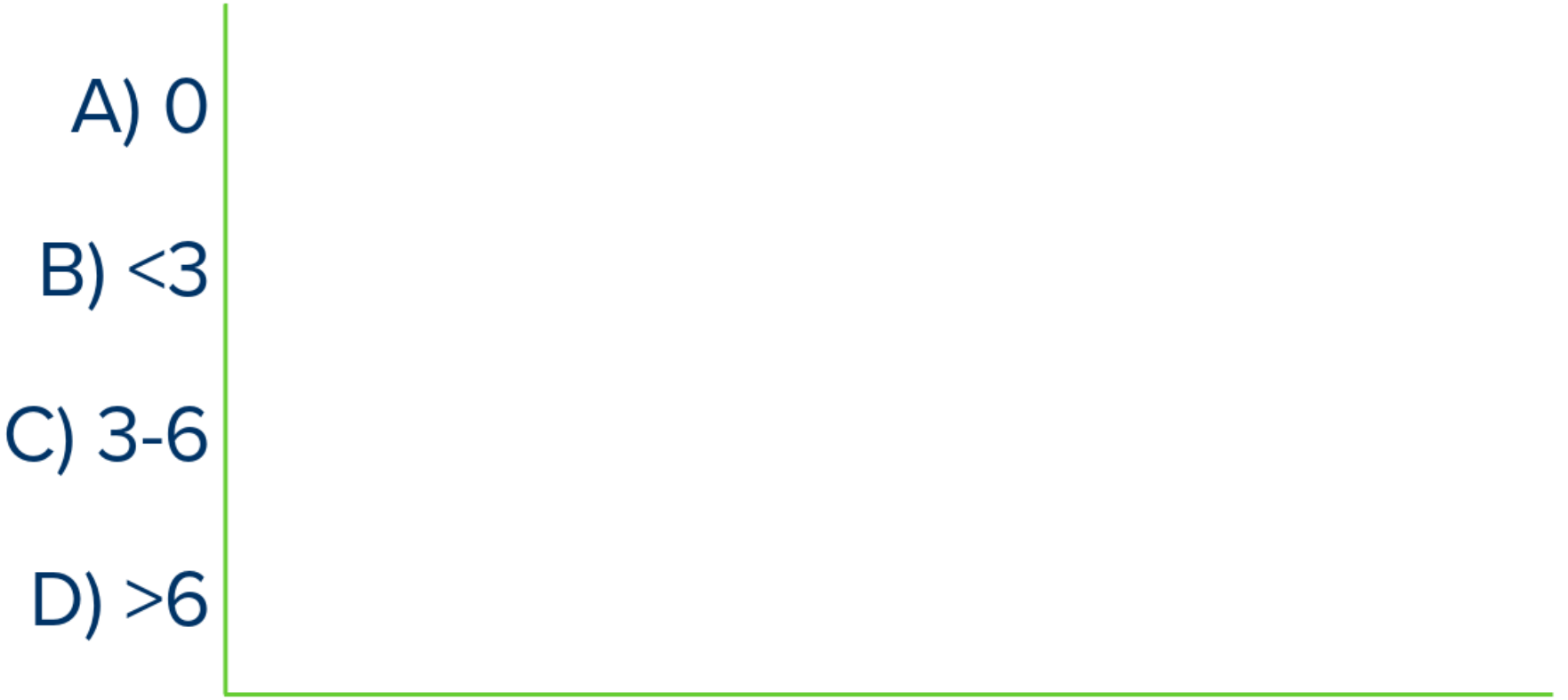
Disclosures

- Meena Ramchandani does not have relationships with a commercial interest related to the content of this educational activity.

Overview

- Epidemiology
- Signs, symptoms
- Staging of disease
- Lab testing
- Treatment
- Complications
- Links to online learning courses

Just a rough estimate, to get a feel for your practice, how many patients have you seen with syphilis in the last 1-2 months?



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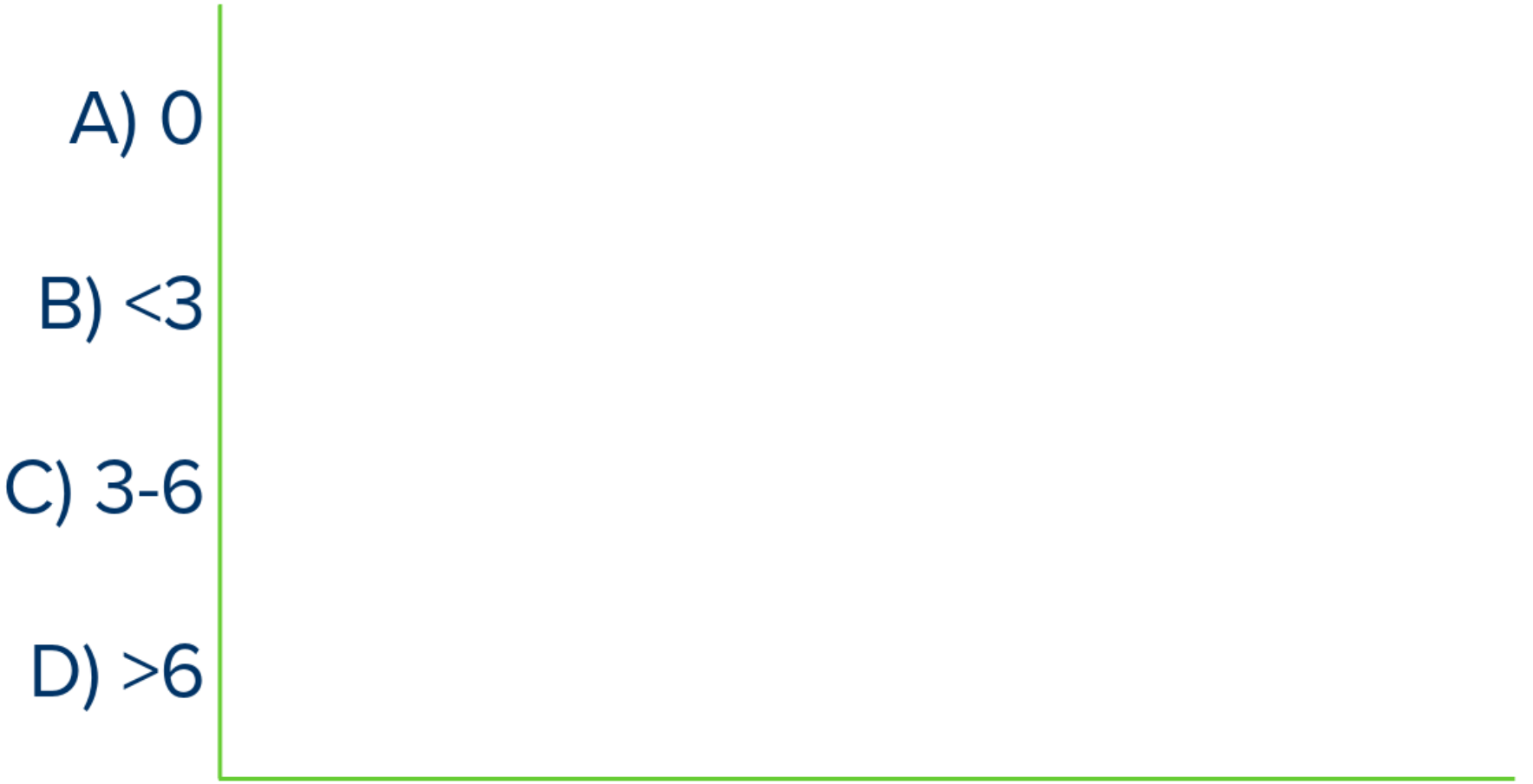
Total Results

How many neurosyphilis cases have you seen or been involved in taking care of?



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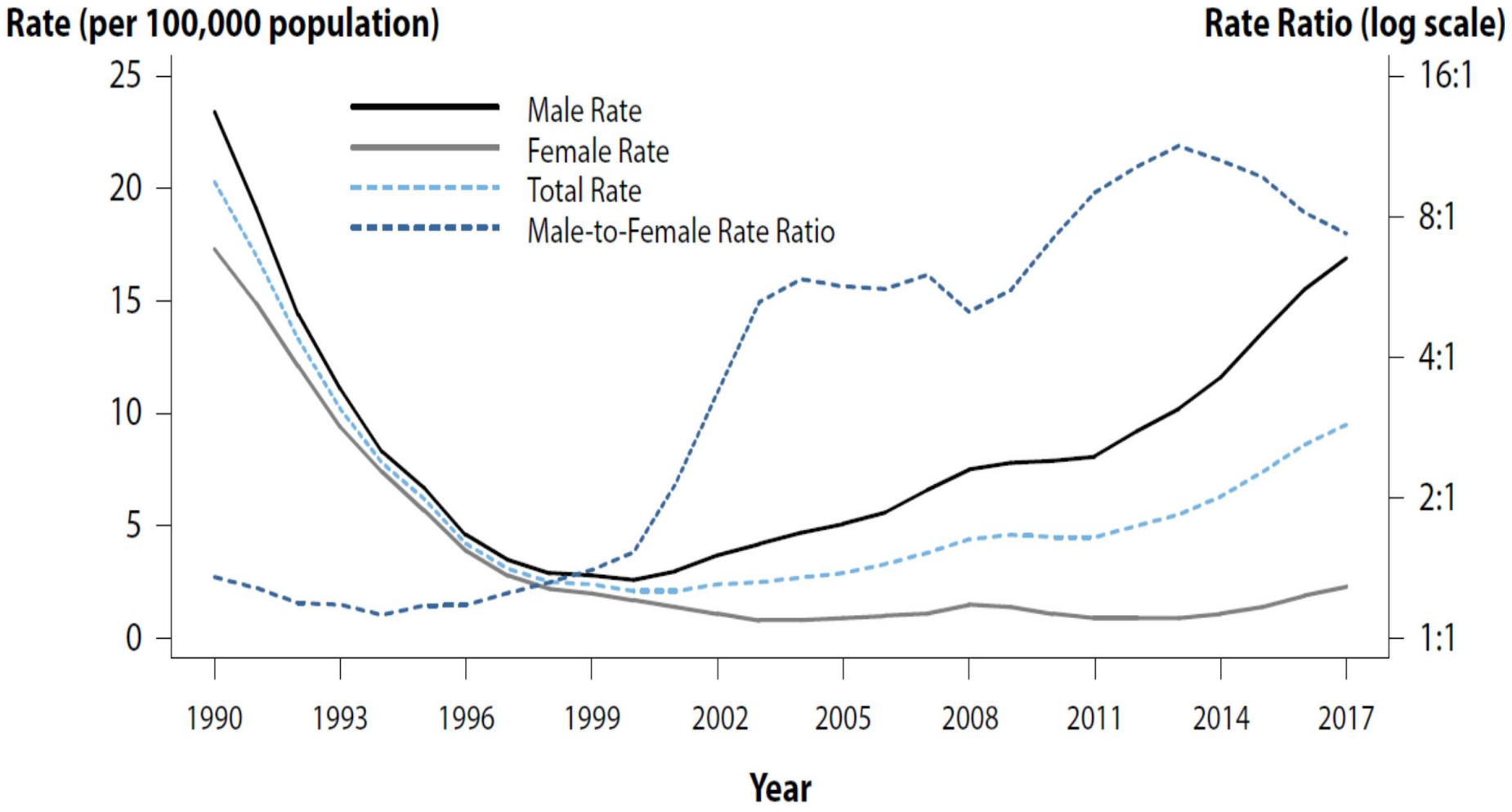
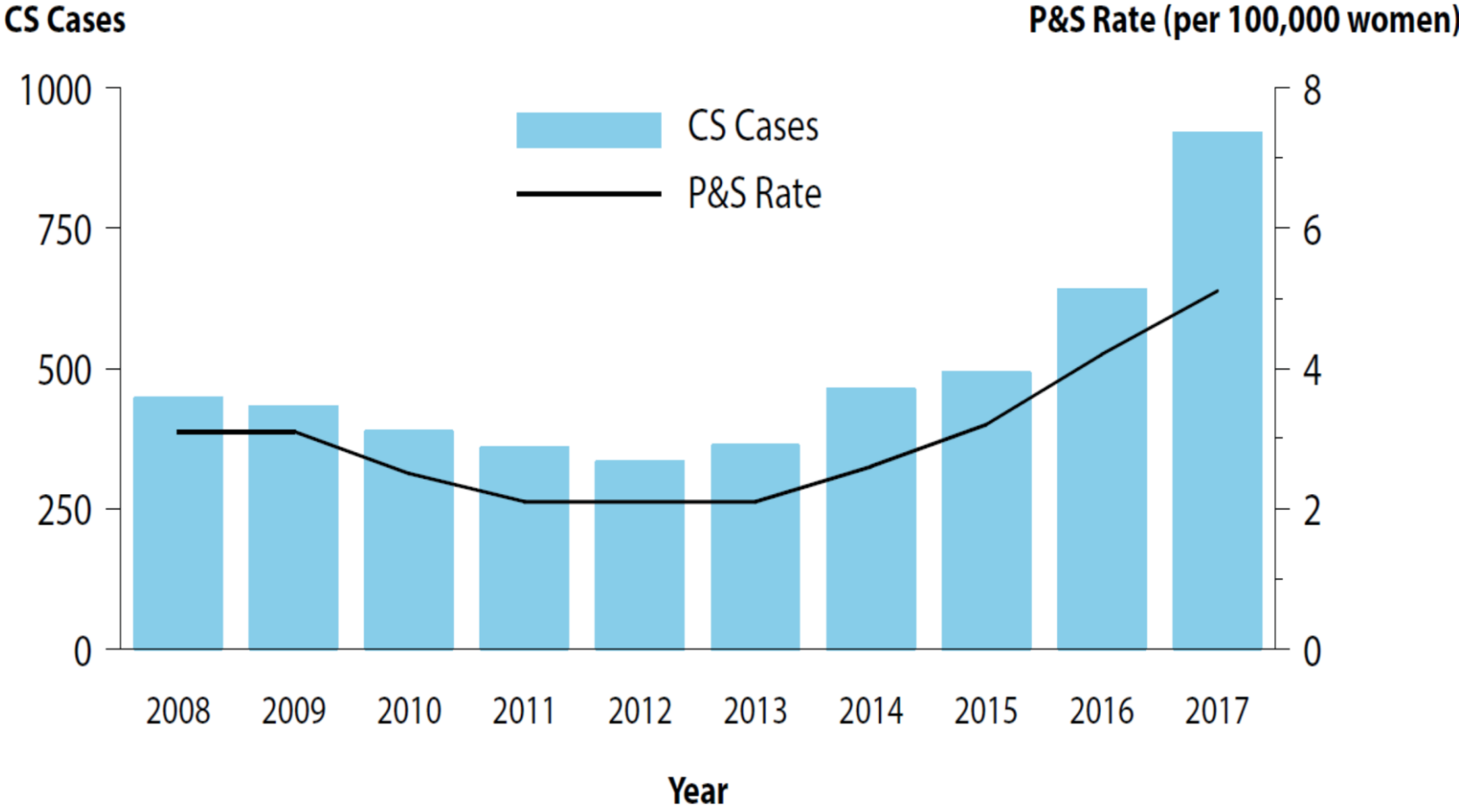
Total Results

Primary and Secondary Syphilis — Rates of Reported Cases by Sex and Male-to-Female Rate Ratios, United States, 1990–2017



- 88% of all P&S syphilis cases in the U.S. in 2017 occurred in men
- 80% of male syphilis cases in MSM (when sex of sex partner known)
- However, 2016-2017, cases increased by 25% in women!

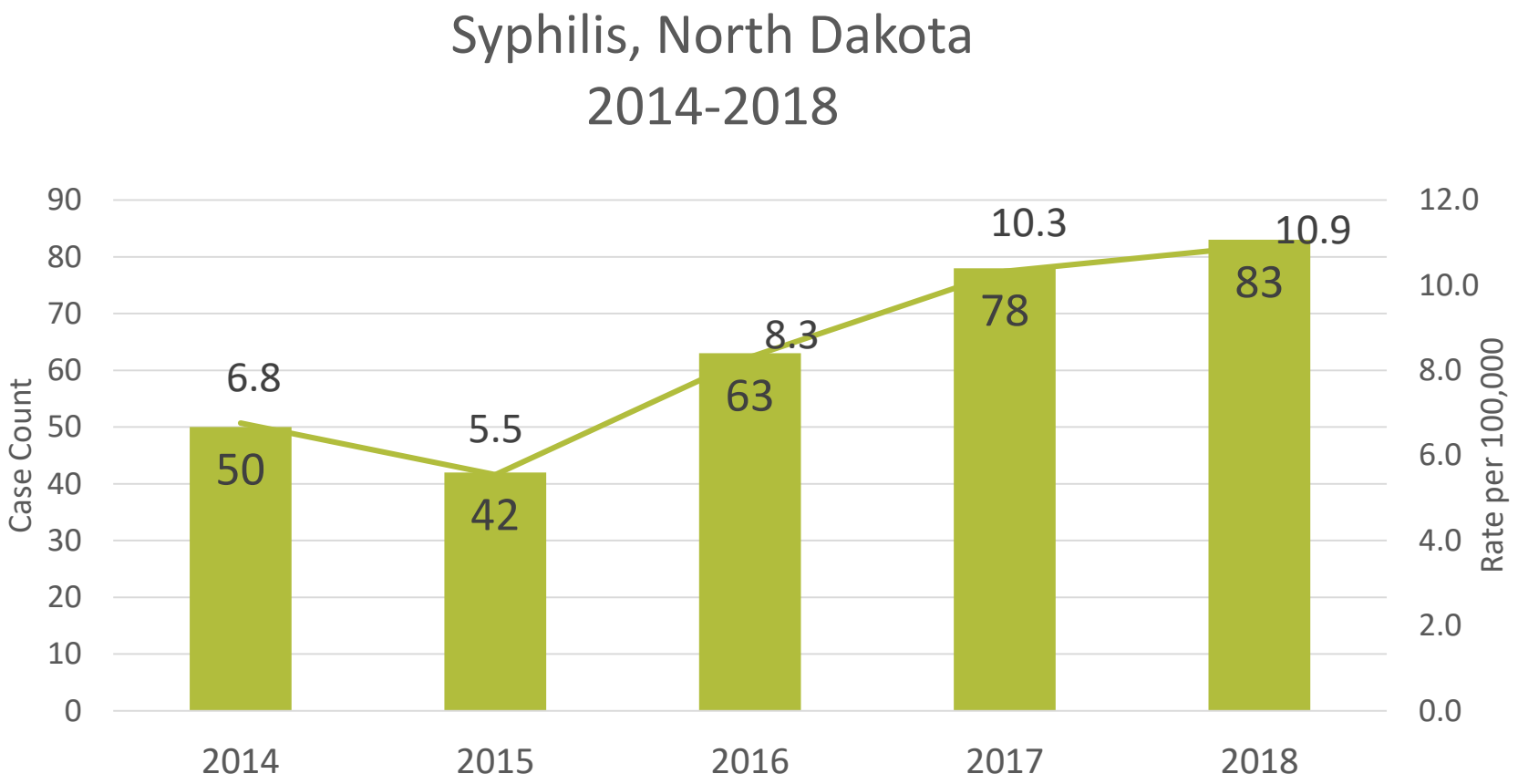
Congenital Syphilis — Reported Cases by Year of Birth and Rates of Reported Cases of Primary and Secondary Syphilis Among Women Aged 15–44 Years, United States, 2008–2017



- **918 cases of congenital syphilis in the US in 2017 (~600 in 2016)**
- **64 still births (41 in 2016)**
- **Repeat RPR in 3rd trimester - >1 partner, nonmongamous partners, substance use, homeless**

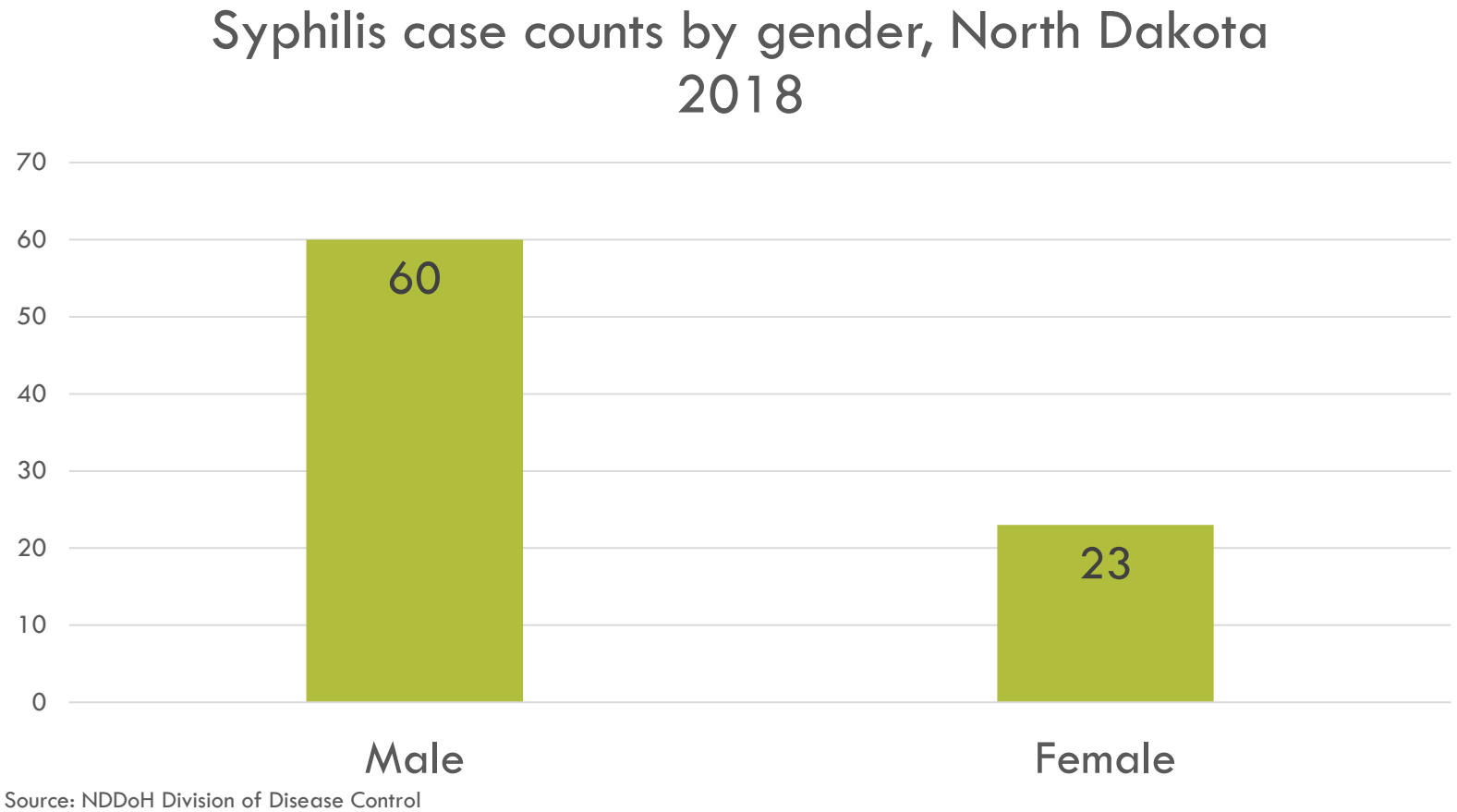
ACRONYMS: CS = Congenital syphilis; P&S = Primary and secondary syphilis.

Syphilis infections (all stages) increased 6.4% in 2018



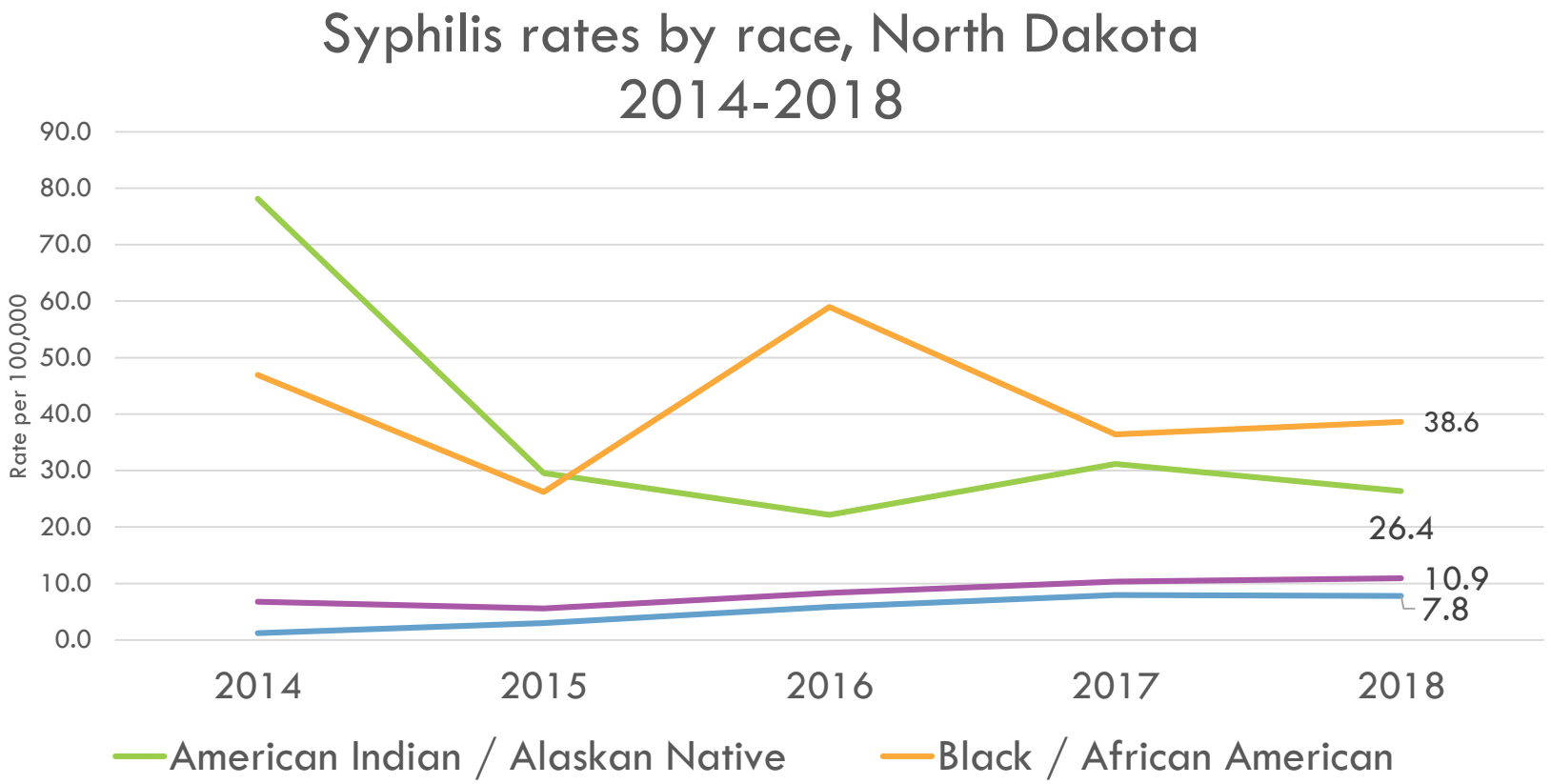
Source: NDDoH Division of Disease Control

- 72% of syphilis infections were male
  66% of syphilis infections were between 20-34 years old



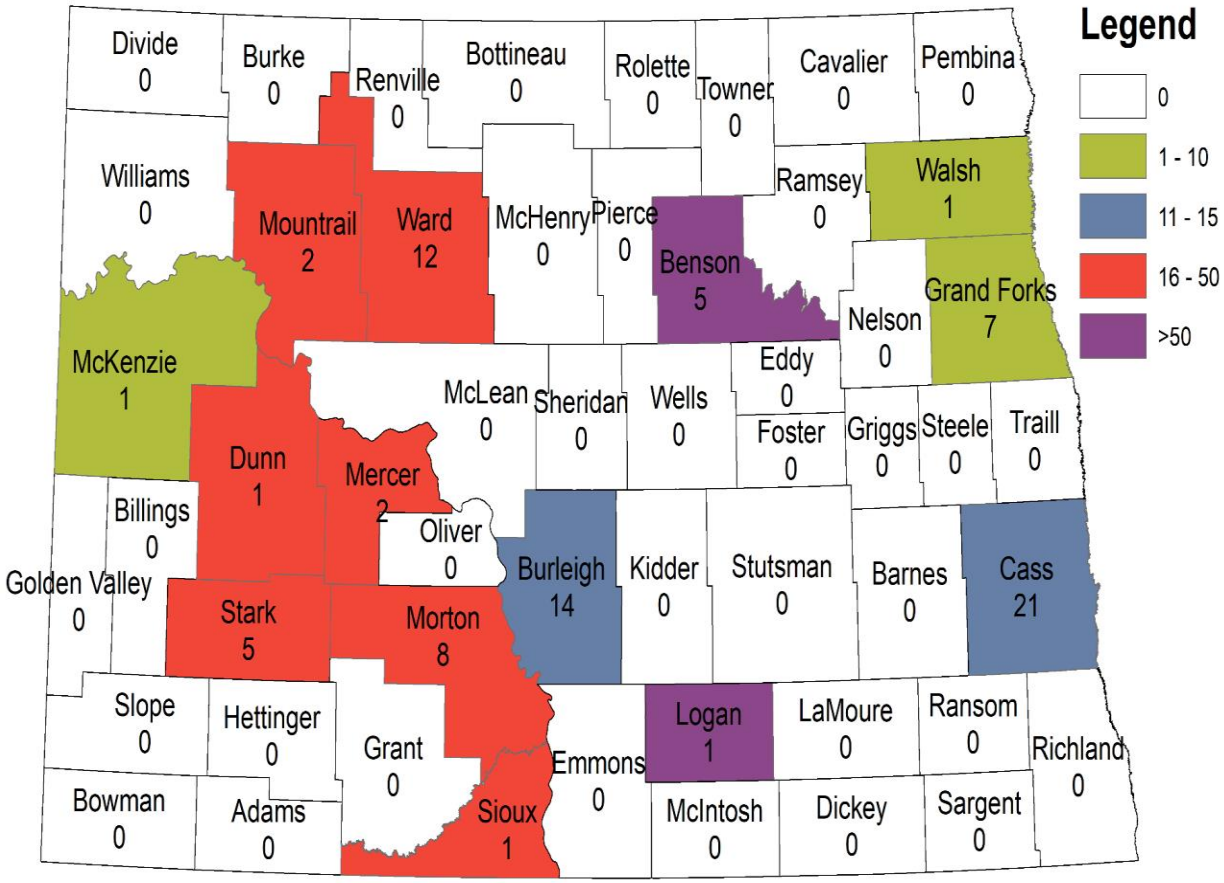
Source: NDDoH Division of Disease Control

Black/African Americans had the highest rate of syphilis in 2018



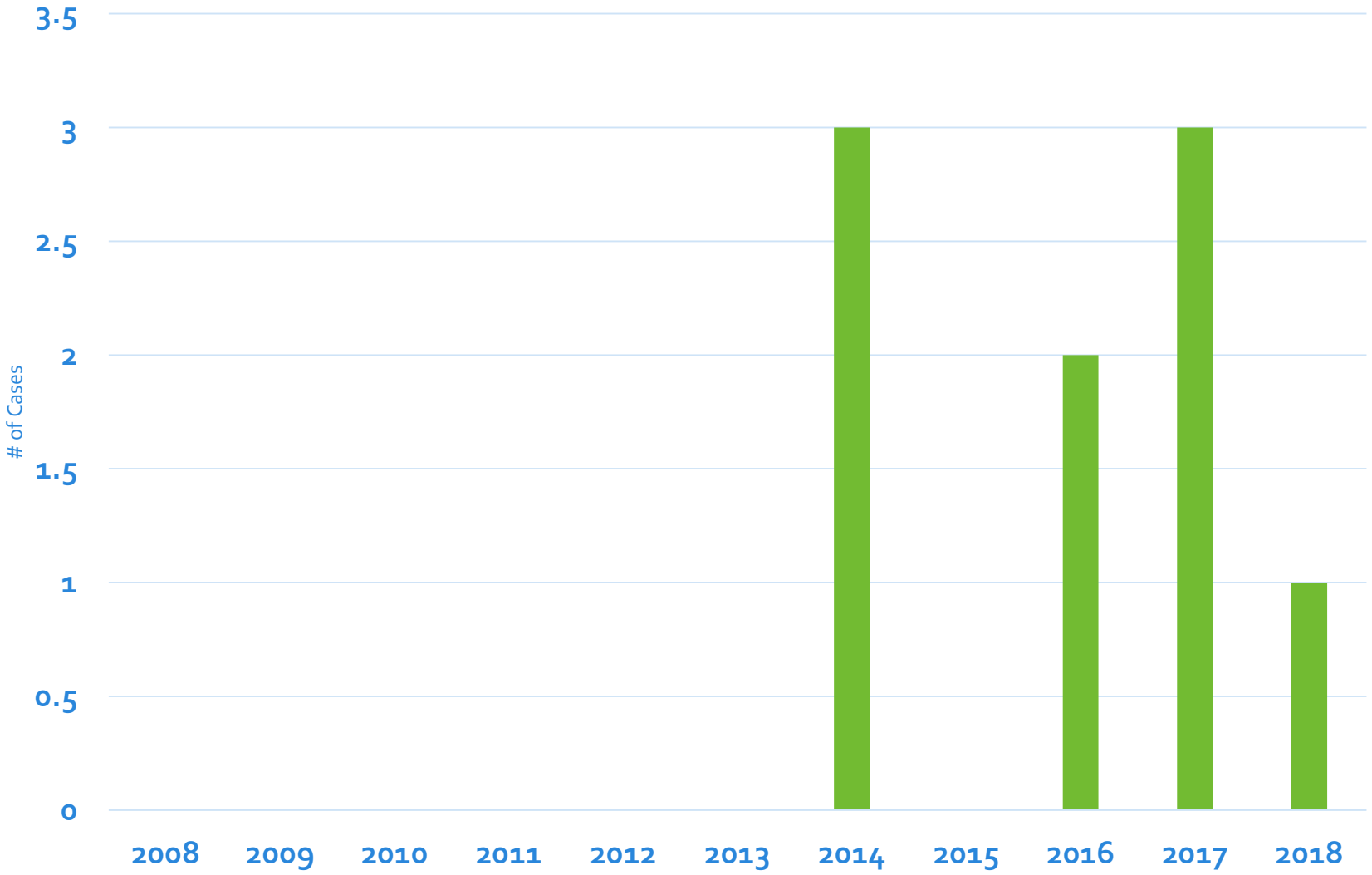
Source: NDDoH Division of Disease Control

Syphilis was reported in 14 counties



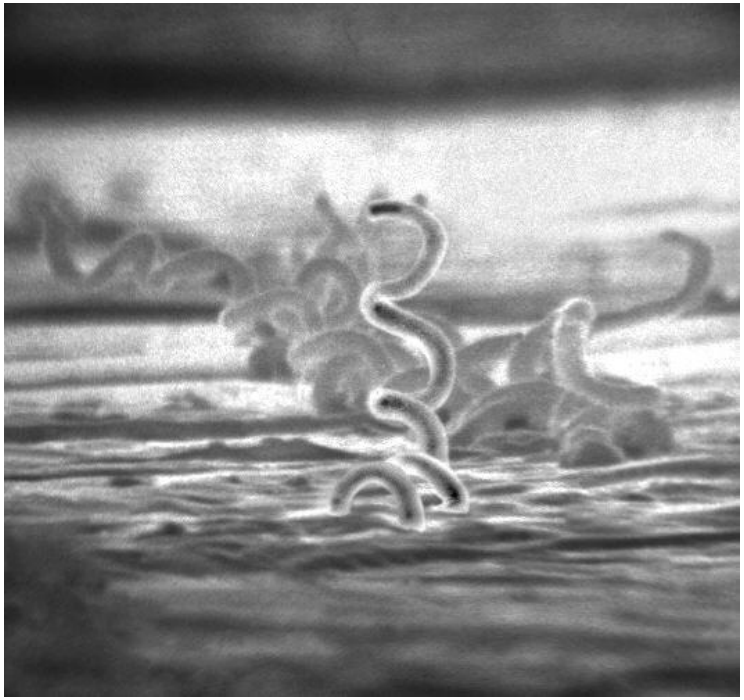
Map is shaded by rate per 100,000 and labeled by case count, 2018

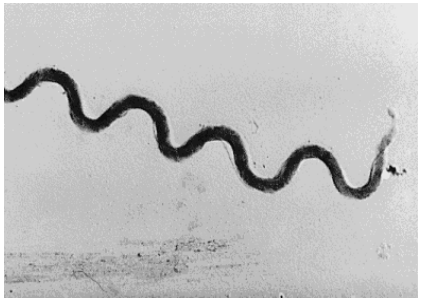
Congenital Syphilis



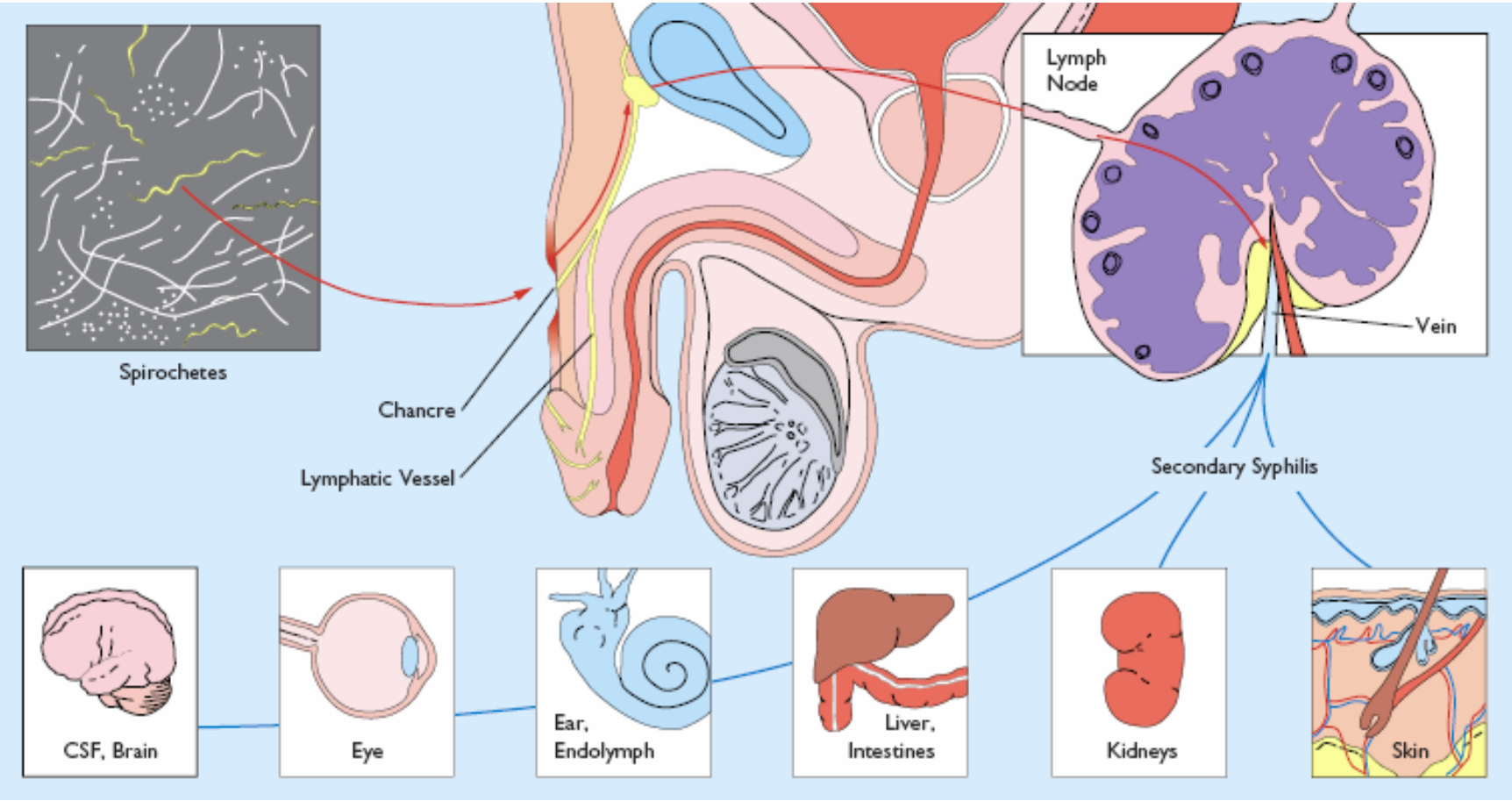
Syphilis Disease: Transmission

- Chronic sexually transmitted infection caused by *Treponema pallidum*
- Infection through small breaks in skin or mucous membranes
- Risk of developing syphilis after sexual contact 10-60% (average about 30%)
- Highest risk with contact to early syphilis; Lesions with many treponemes transmit most effectively.





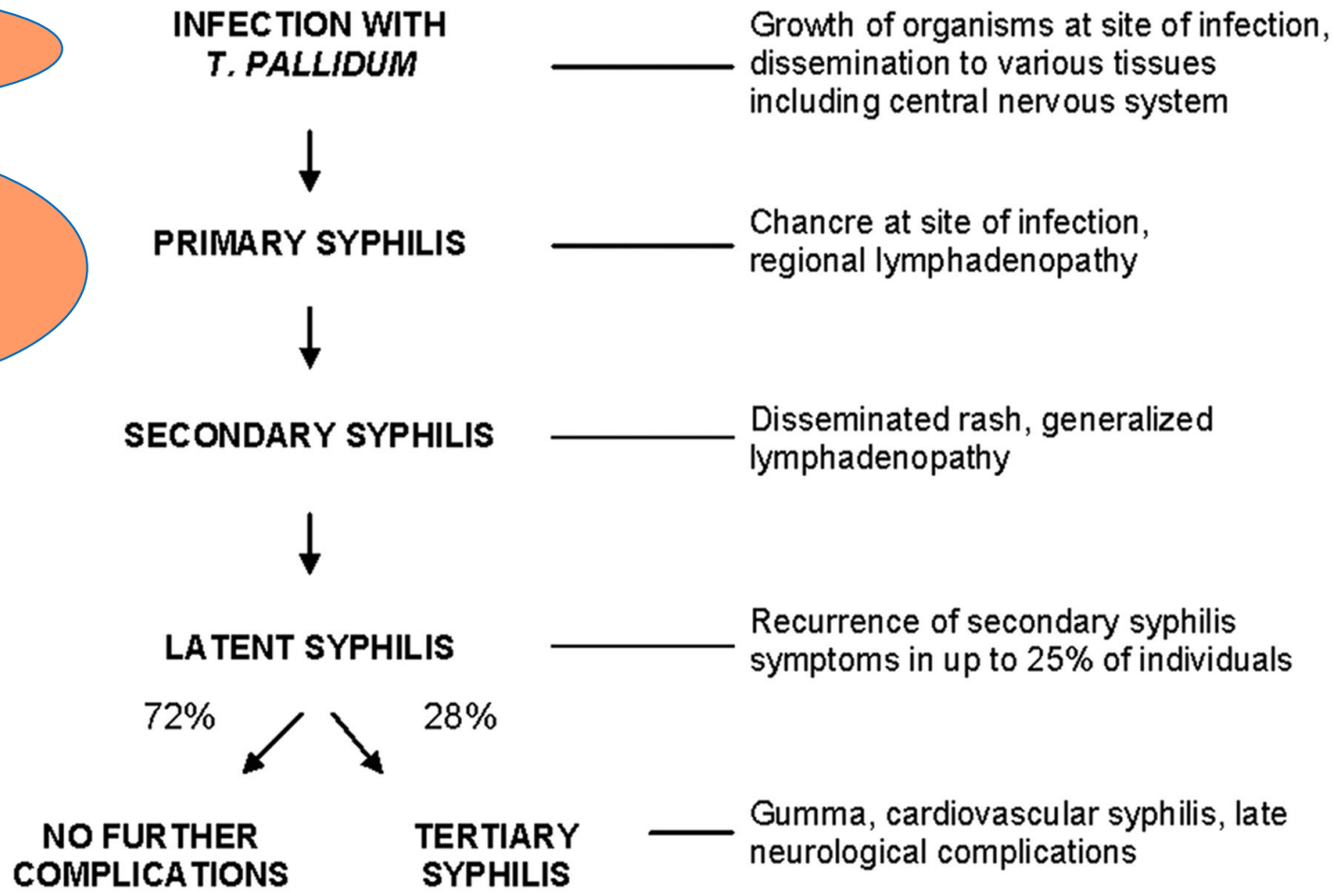
Rapid Dissemination of Syphilis via the Lymphatics and Blood



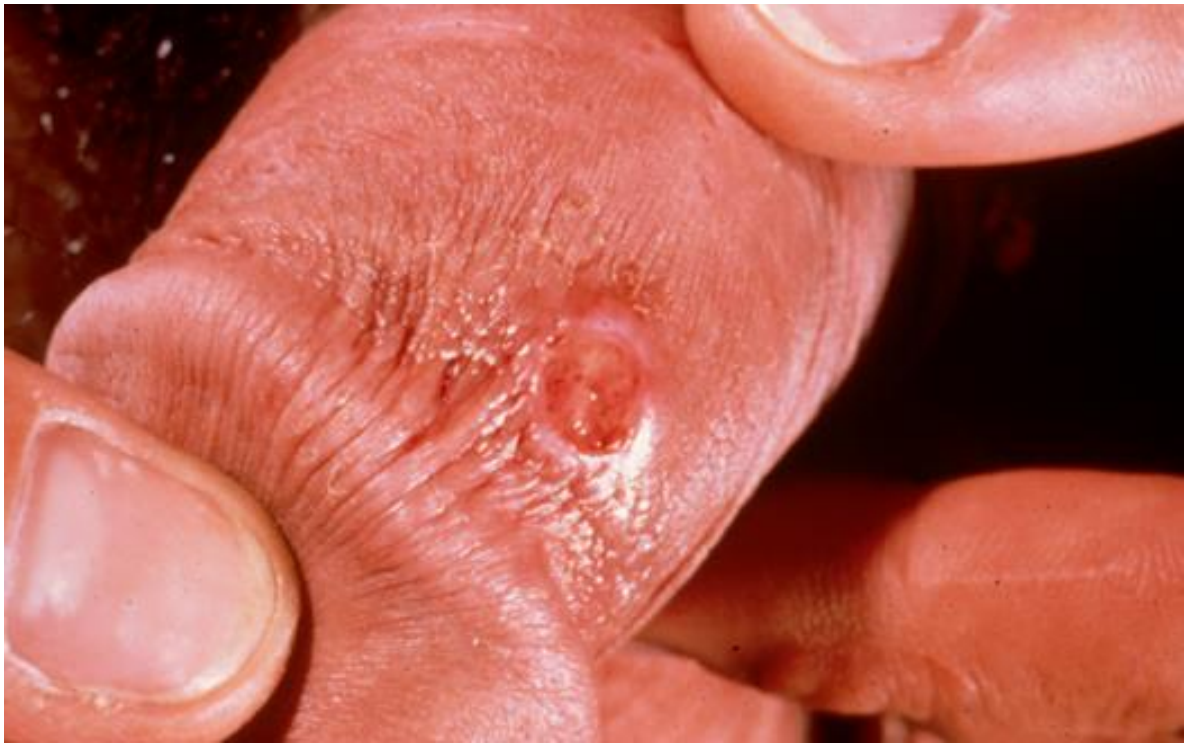
Syphilis – A Brief Refresher

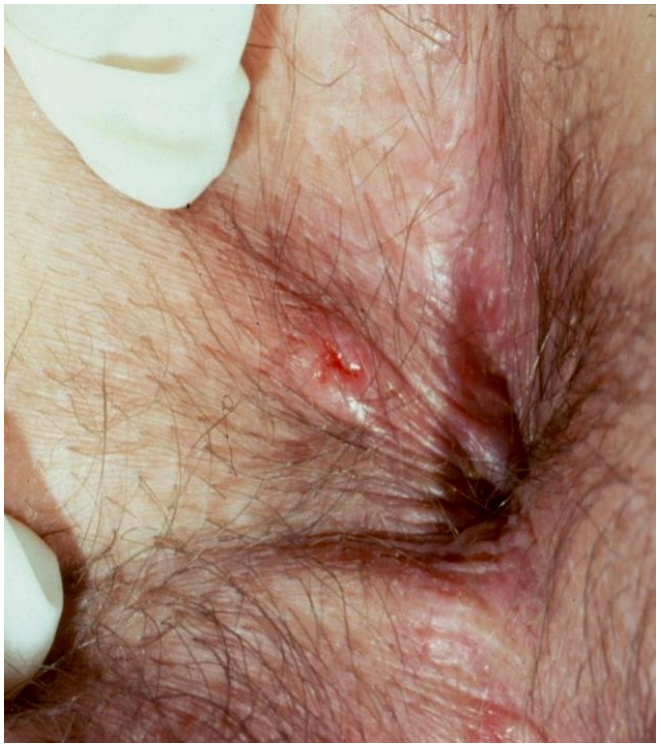
Few hours: mucosal surface -> lymph -> bloodstream

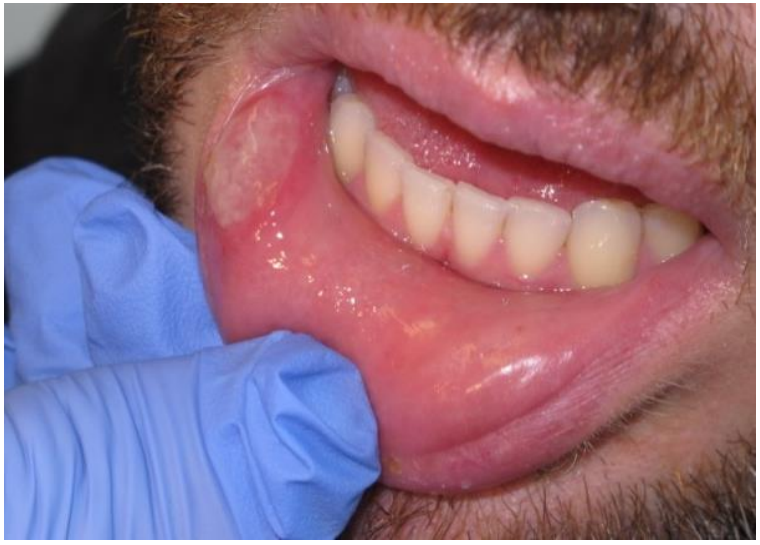
Chancre
~ 3 weeks (10-90 days)
spontaneously heals
1-6 weeks later

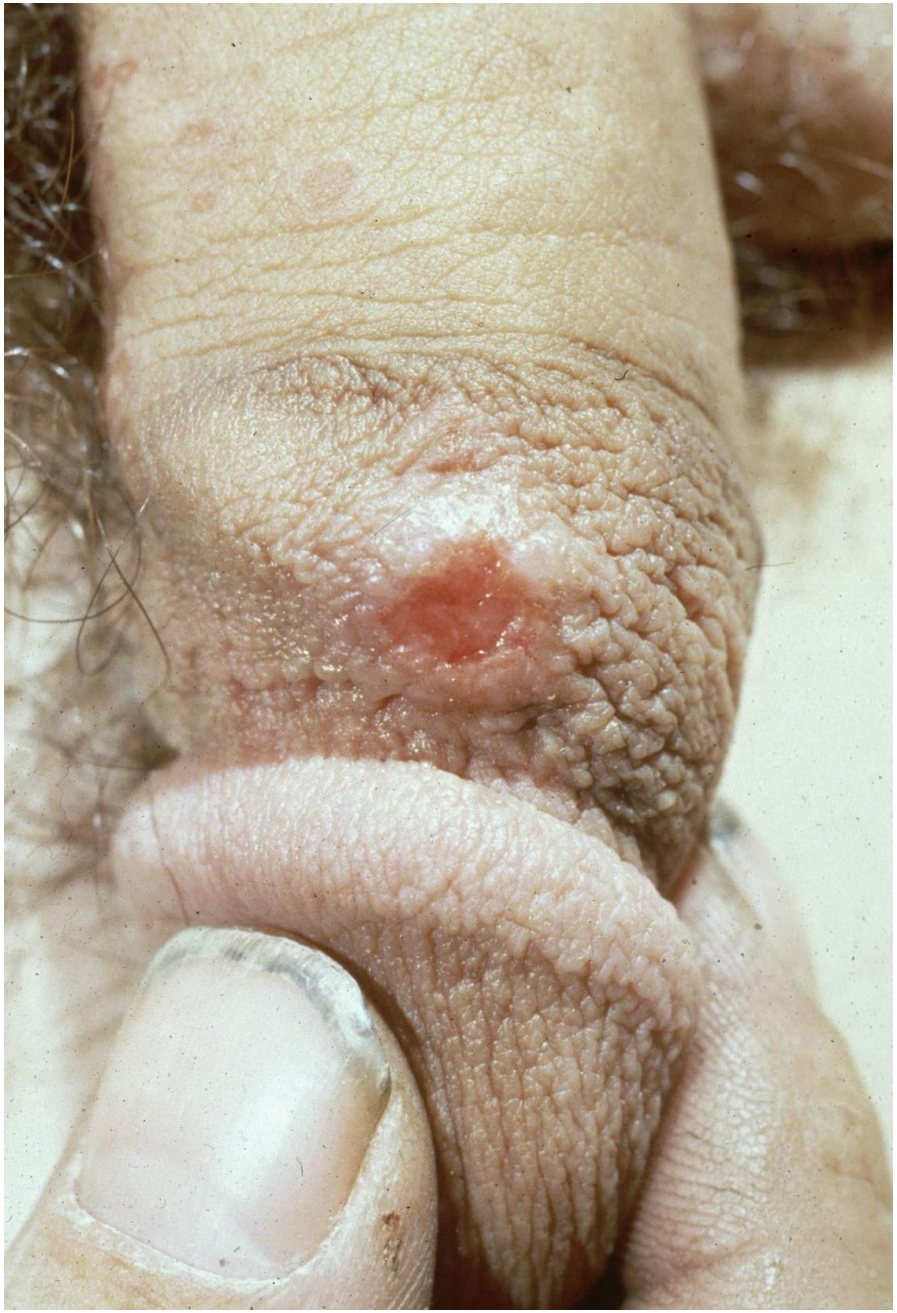


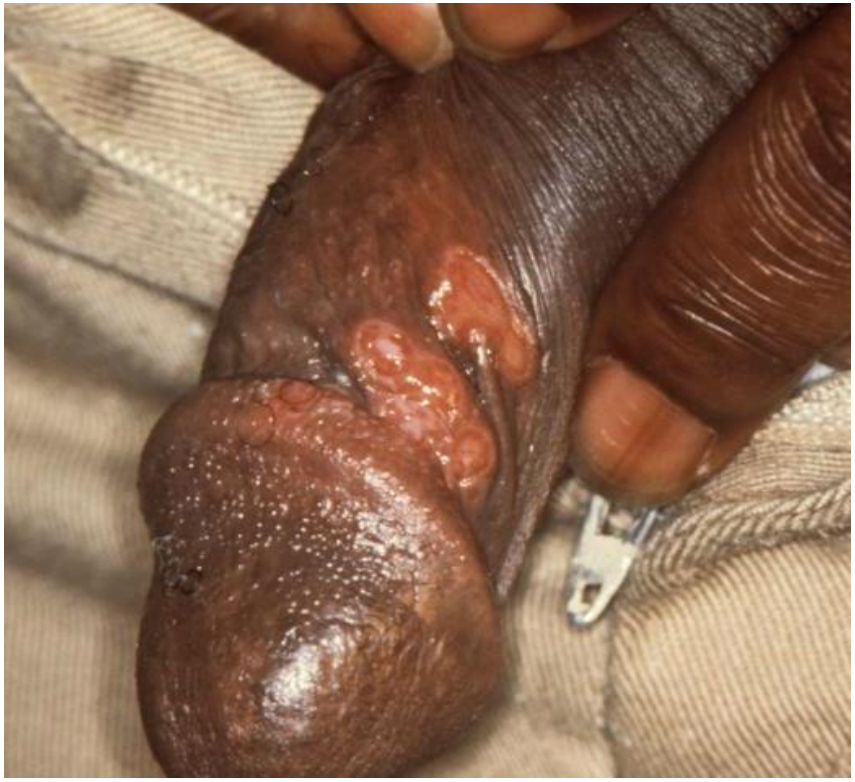
Primary Syphilis

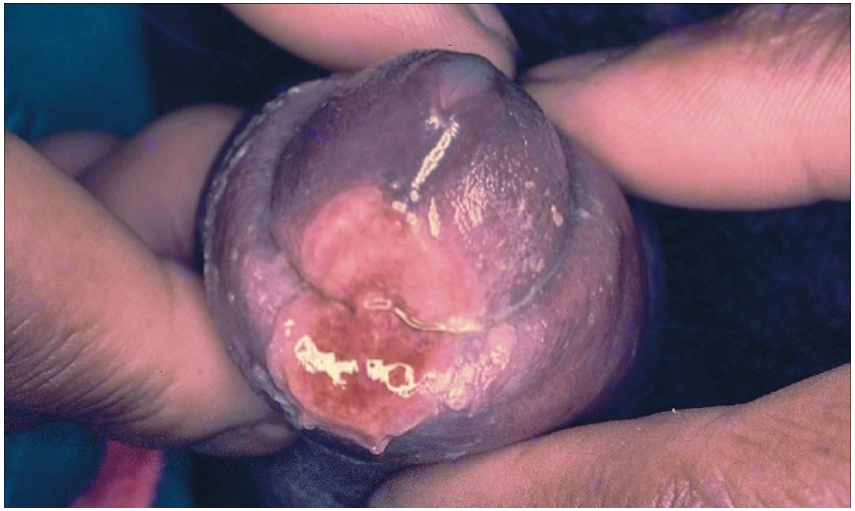




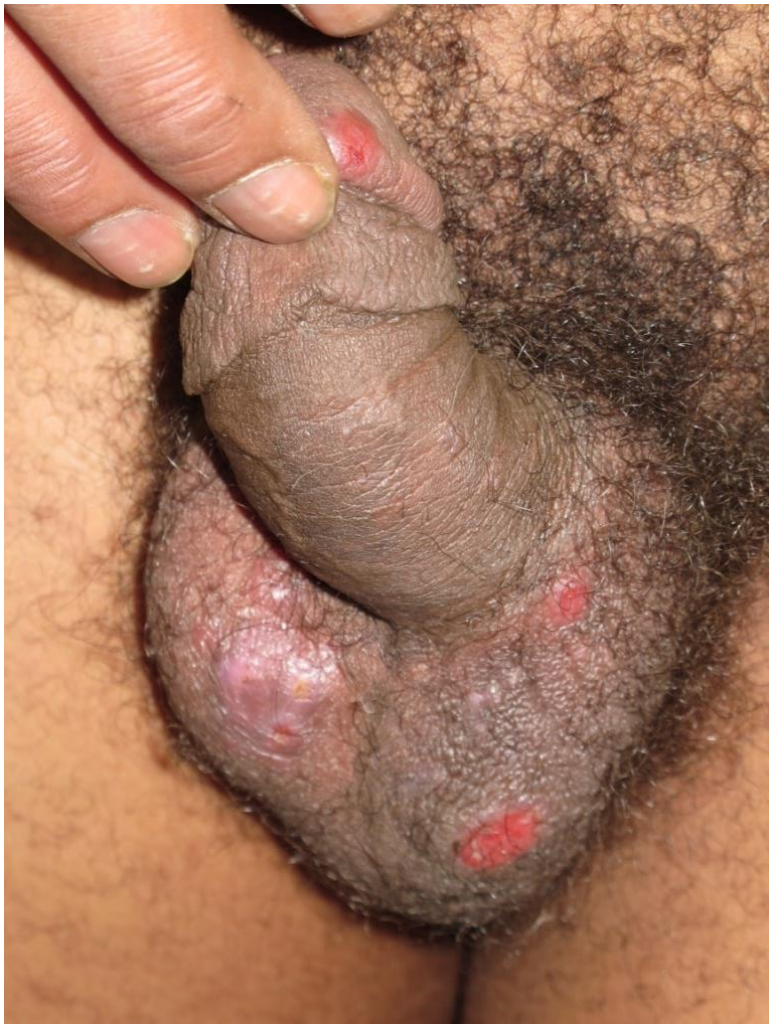


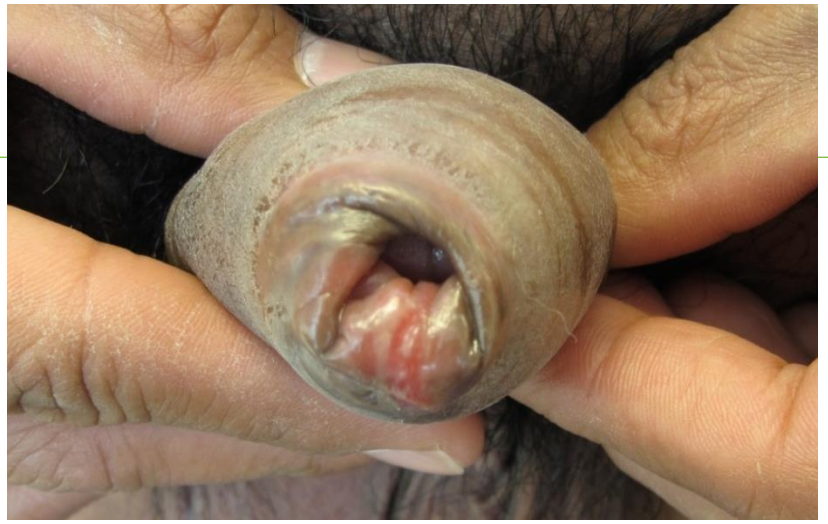


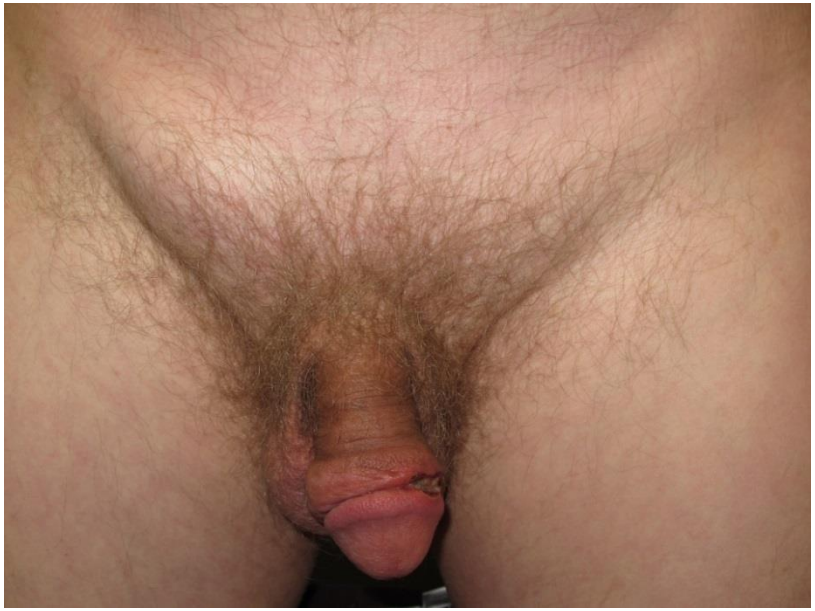




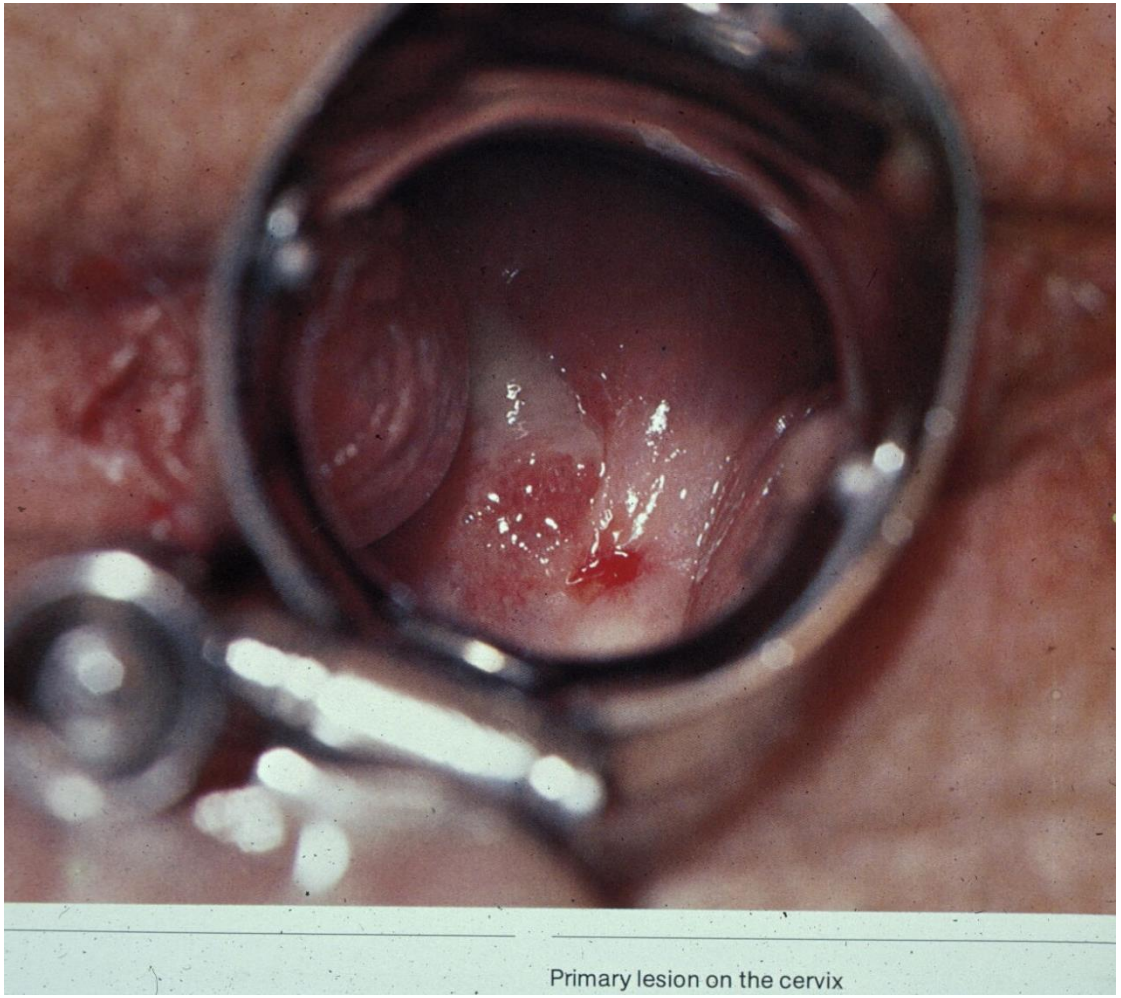
Atypical Primary Syphilis







Chancre



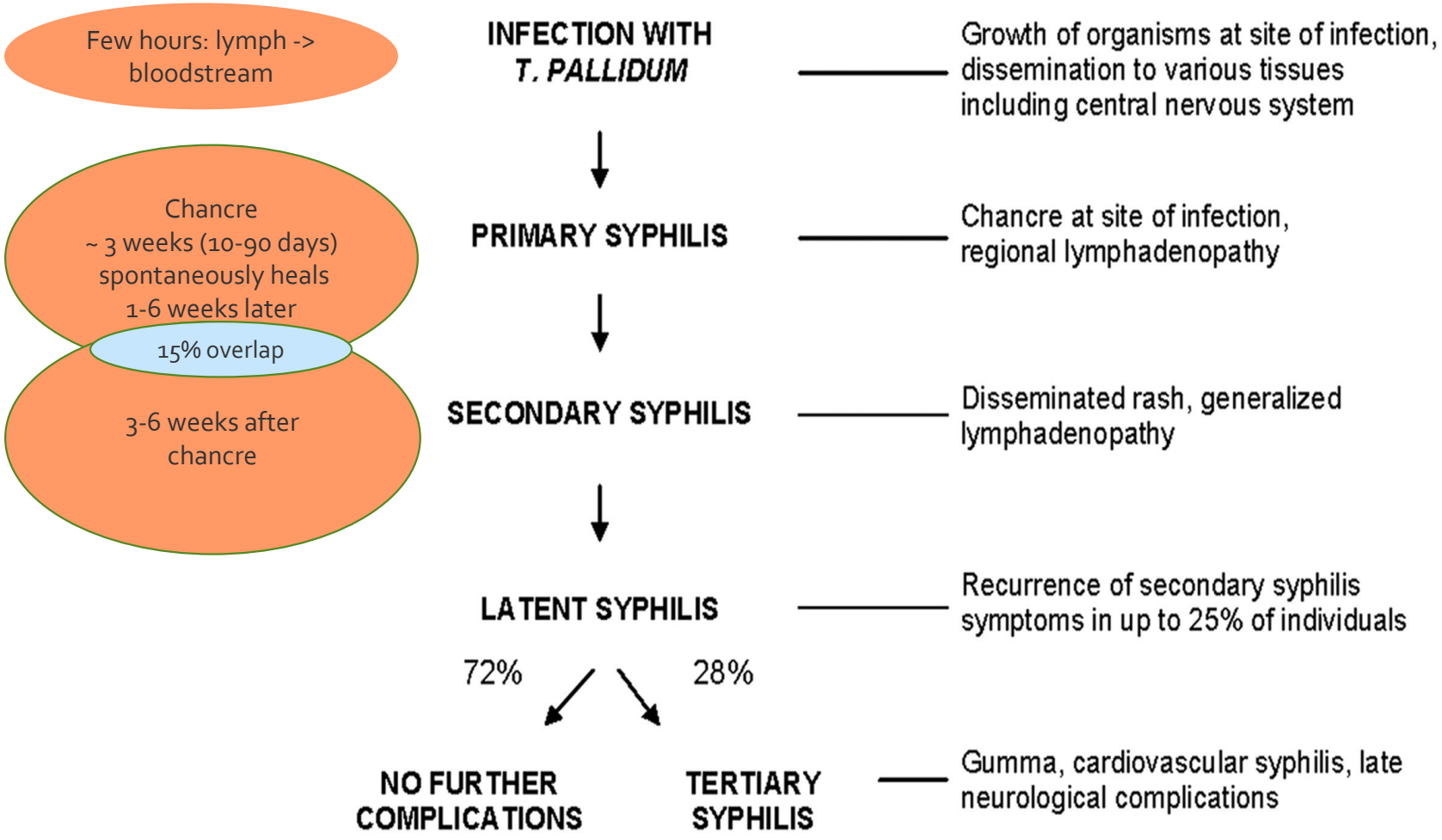
Primary lesion on the cervix

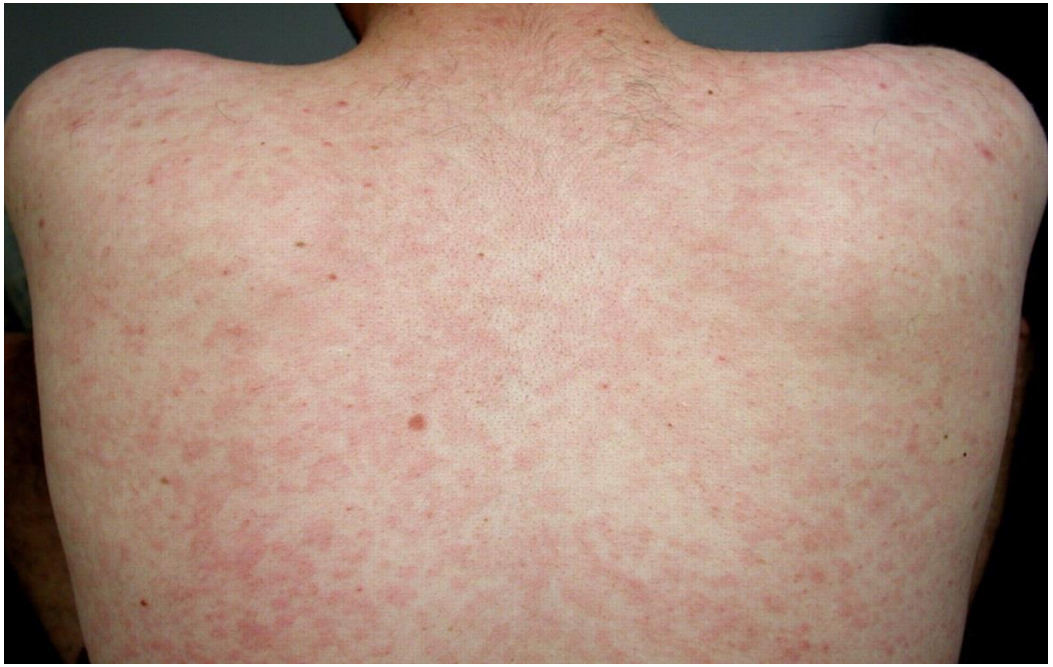
Typical Primary Syphilis

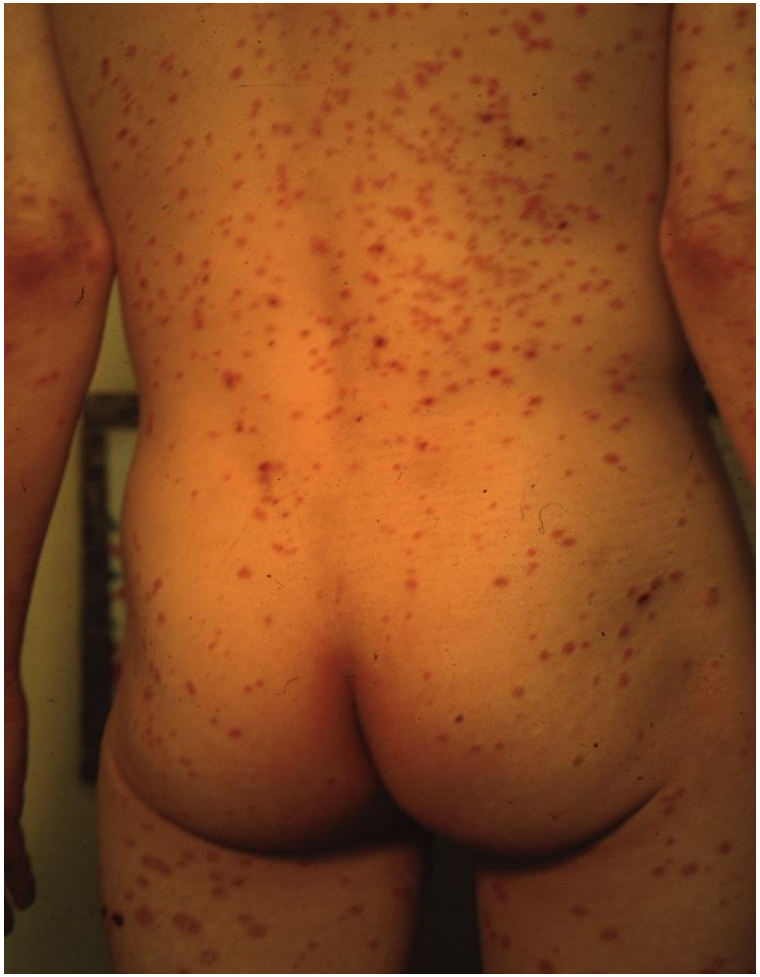
- Nontreponemal tests (RPR, VDRL) **negative** in 15-25% cases of primary syphilis
- Chancres can occur anywhere inoculated by direct contact (fingers, mouth)
- Don't need definitive diagnosis to treat: if you think it's early syphilis → TREAT. Loss to follow up and spread of infection can be high.

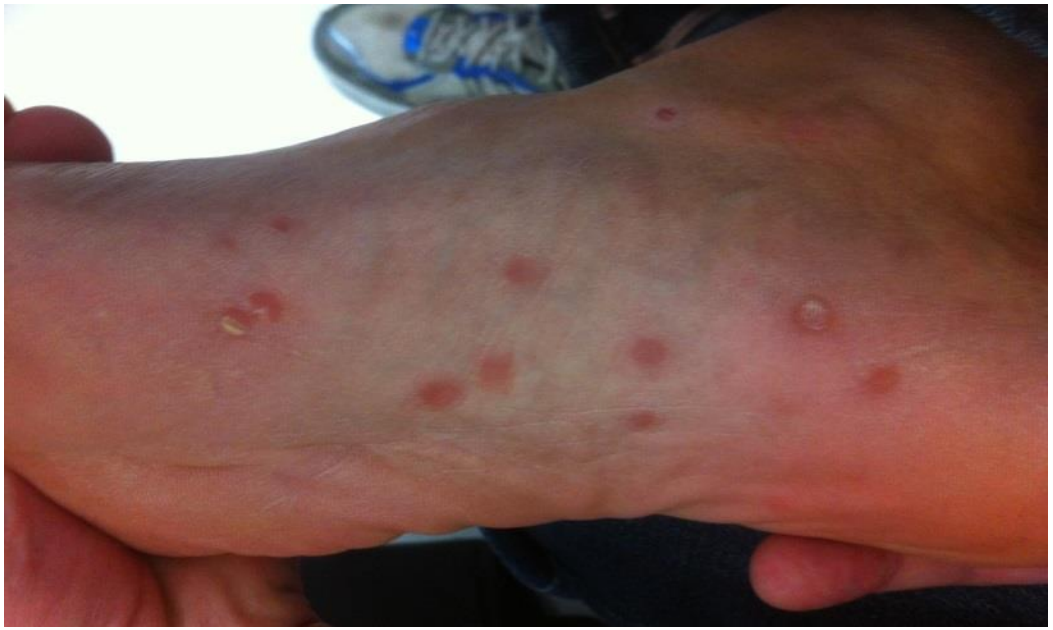
Secondary Syphilis

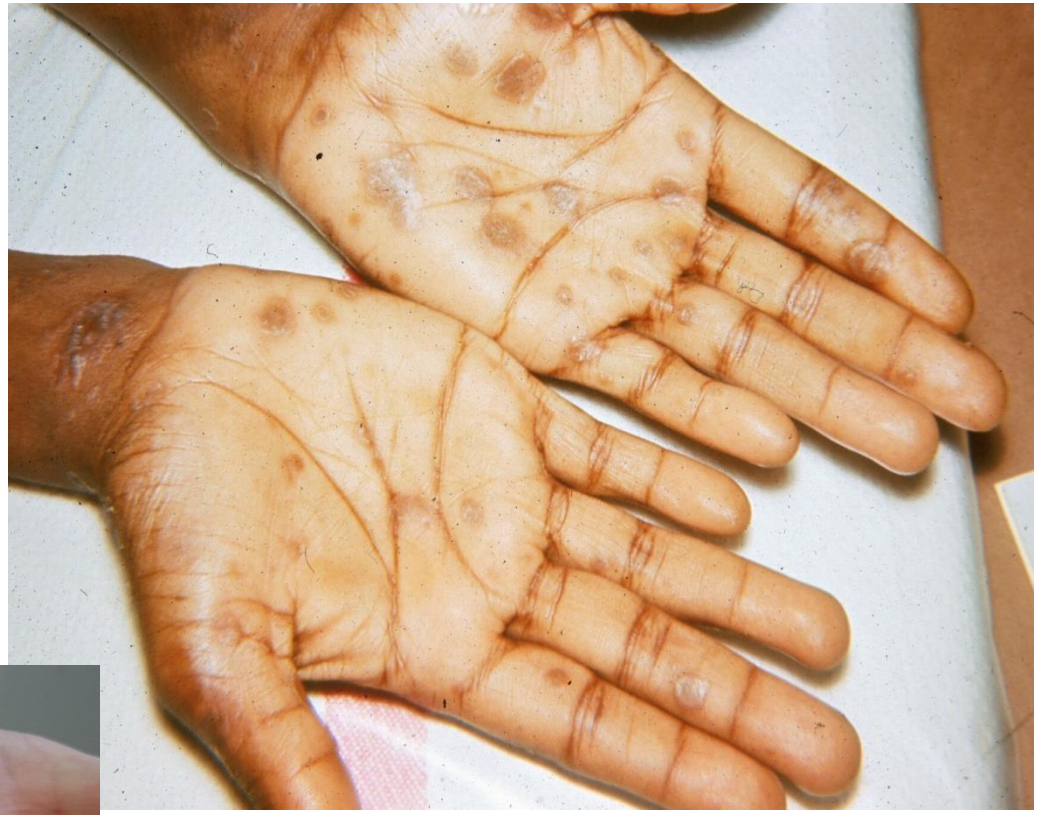
Syphilis – A Brief Refresher

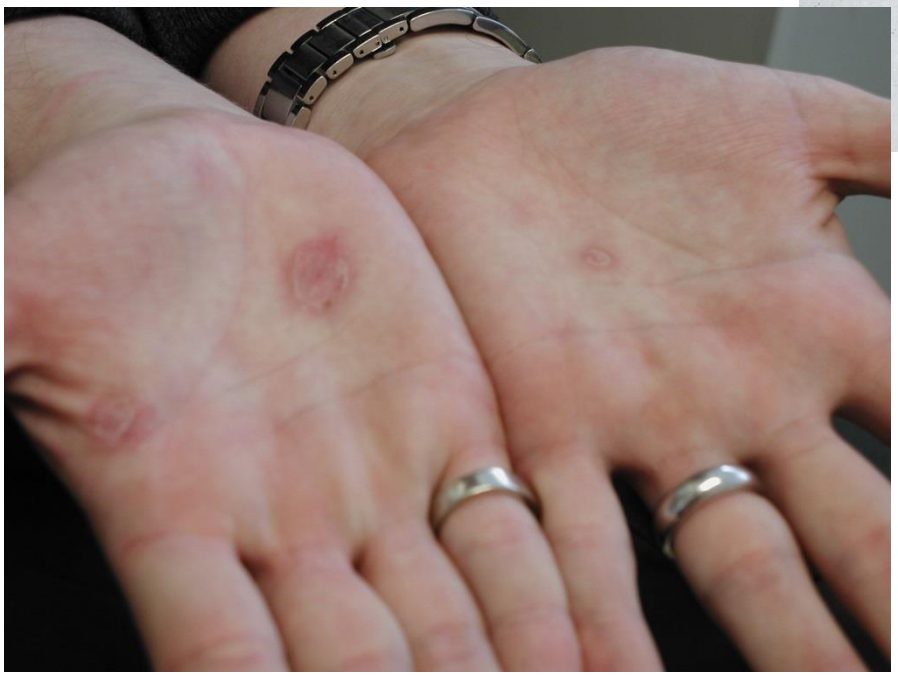






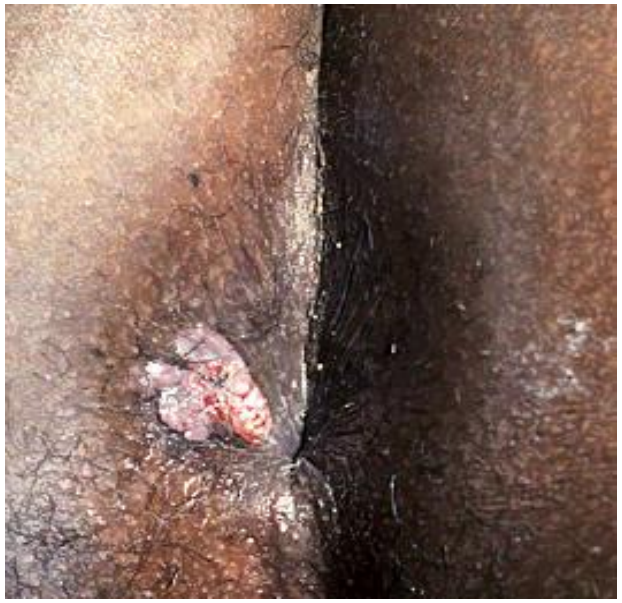


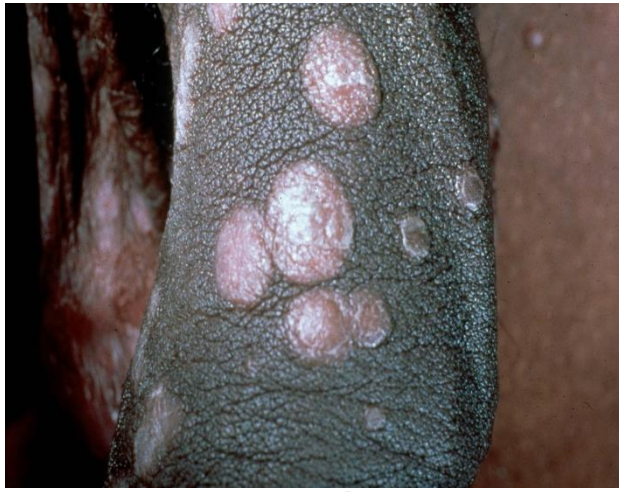




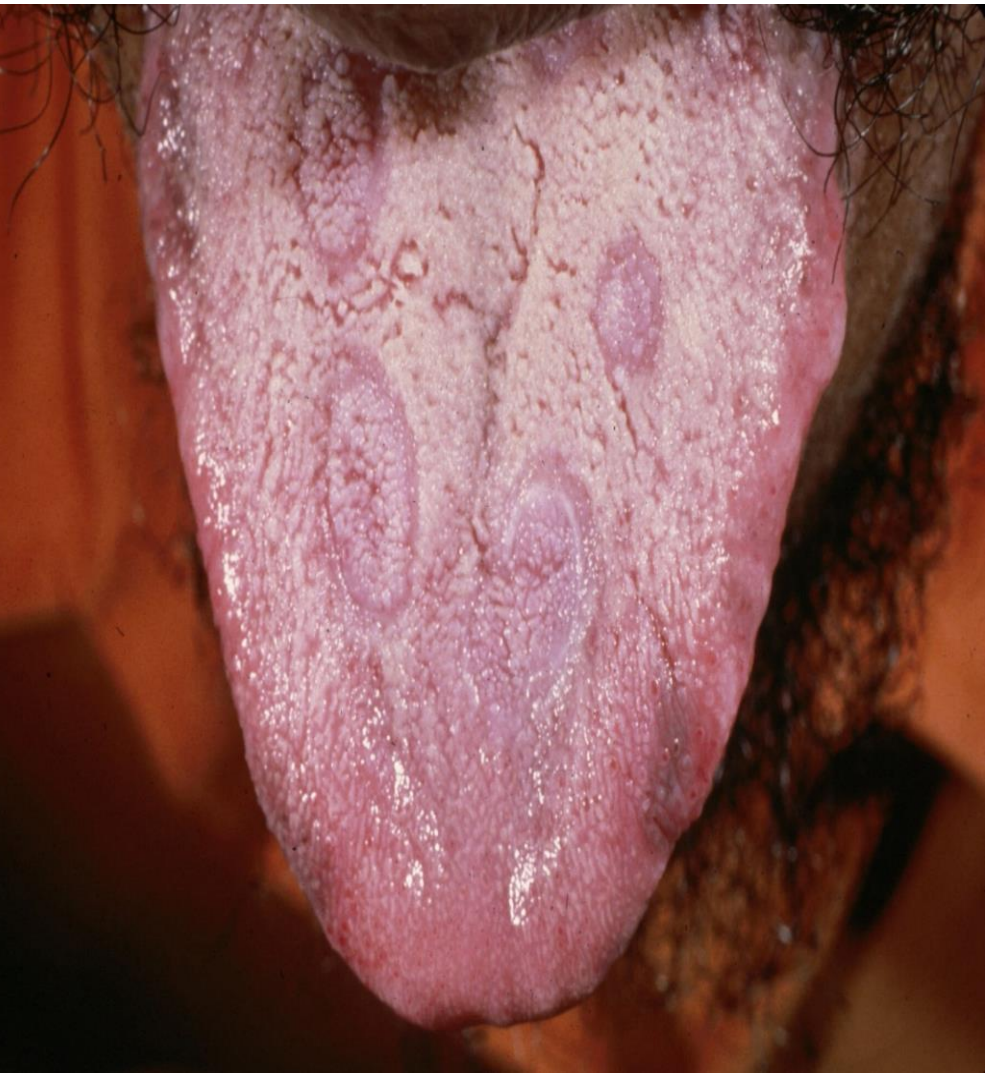
Secondary/Systemic Syphilis: Condyloma lata

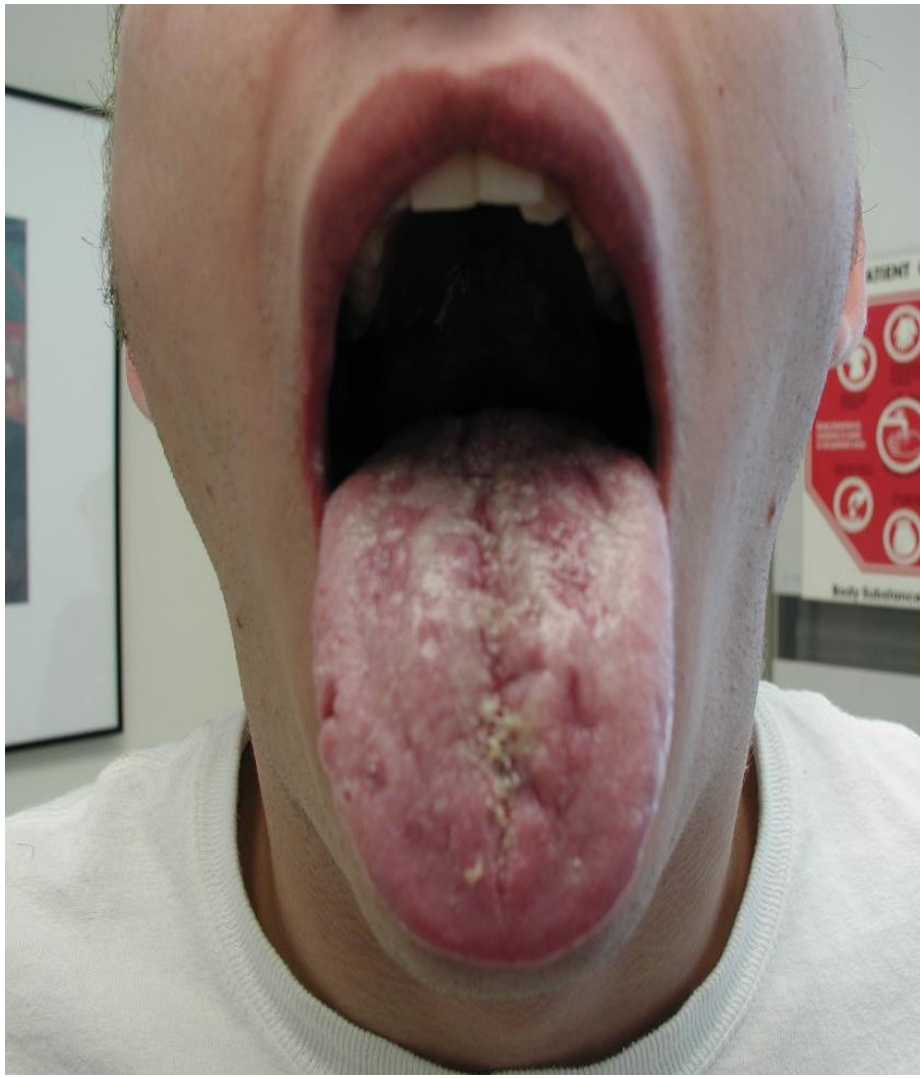
- High numbers of treponemes
- May occur at any moist body site
- Highly contagious
- Fleshy, flat-topped appearance may help distinguish from warts, but often mistaken for latter
- Pearl: WET warts generally aren't warts!





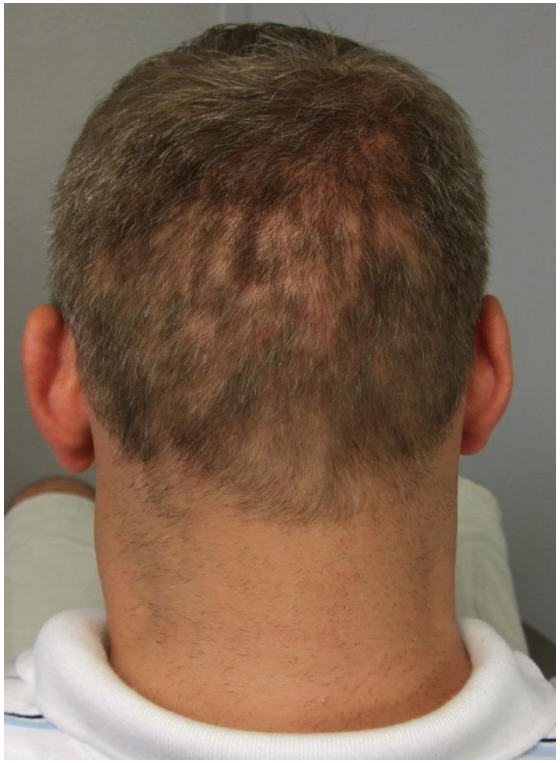
Secondary Syphilis: Mucous patches

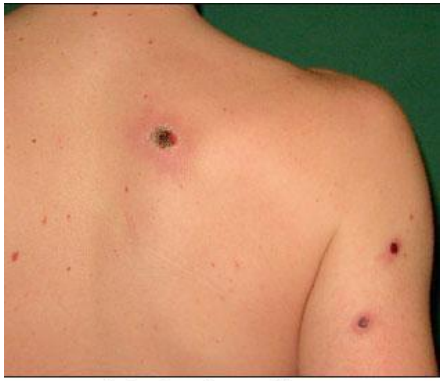




Secondary Syphilis: Less common

- Alopecia (5%)
  - Due to infection of hair follicles
  - Patchy, “moth-eaten”
  - loss of lateral eyebrows
- Liver, kidney, spleen involvement
- Really rare: lues maligna – necrotic skin lesions





Obr. 1 – Kožní projevy lues maligna | Foto: archiv autora

Patient Case

- Your patient is a 37 year old male to female who presents to your clinic for routine testing.
- She has no symptoms, but has a positive RPR titer of 1:8 found on routine screening.
- Her confirmative TPPA is also reactive.
- She tests on occasion, and her last test was negative 2 years ago.

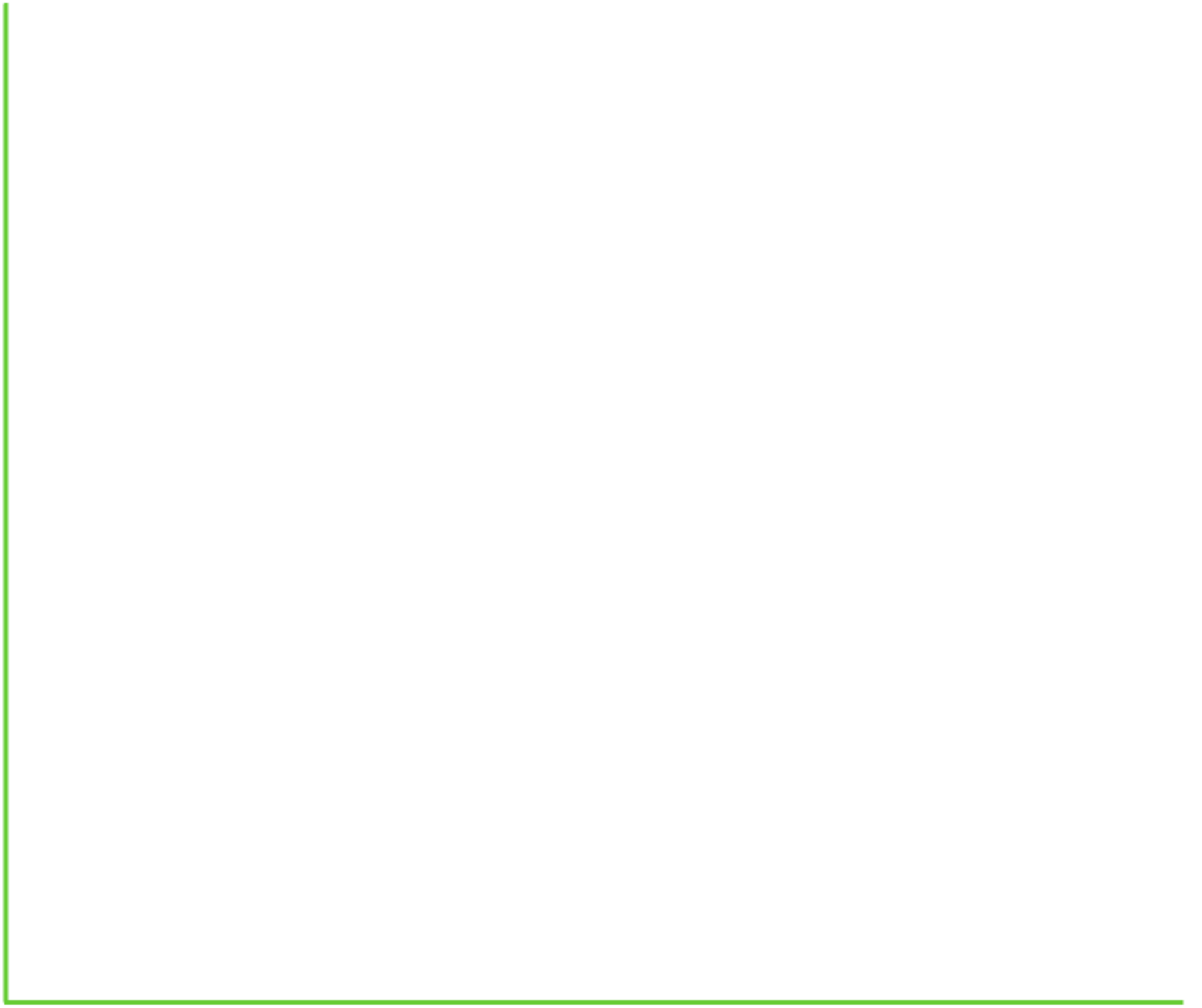
How would you clinically stage her disease?

A) Primary syphilis

B) Secondary syphilis

C) Early latent syphilis

D) Late latent syphilis



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Total Results

Latent Syphilis

Latent Syphilis: New or Old?

- Defined by positive treponemal serology in the absence of clinical manifestations
- Early Latent: Infected less than one year
  - Negative syphilis serology in past year
  - Known contact to an early case of syphilis
- Late Latent (infected > 1 year or unknown duration)
  - No syphilis serology in past year
  - No contact to syphilis case or history of signs/symptoms in past year

Patient Case

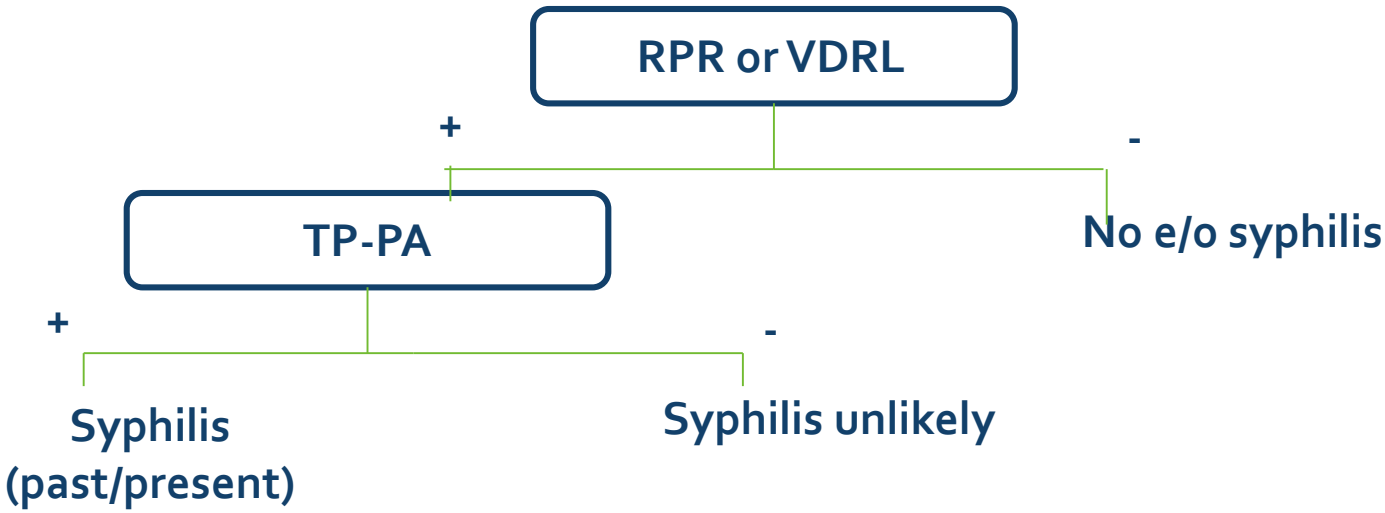
- RPR titer of 1:8, what does that mean?
- Why the TPPA?

Serological Testing for Syphilis

Nontreponemal	Treponemal
	
RPR, VDRL	MHATP, FTA-ABS, TPPA, EIA/CIA
(Quantitative, goes down with treatment)	(Good for screening but once positive, positive for life)

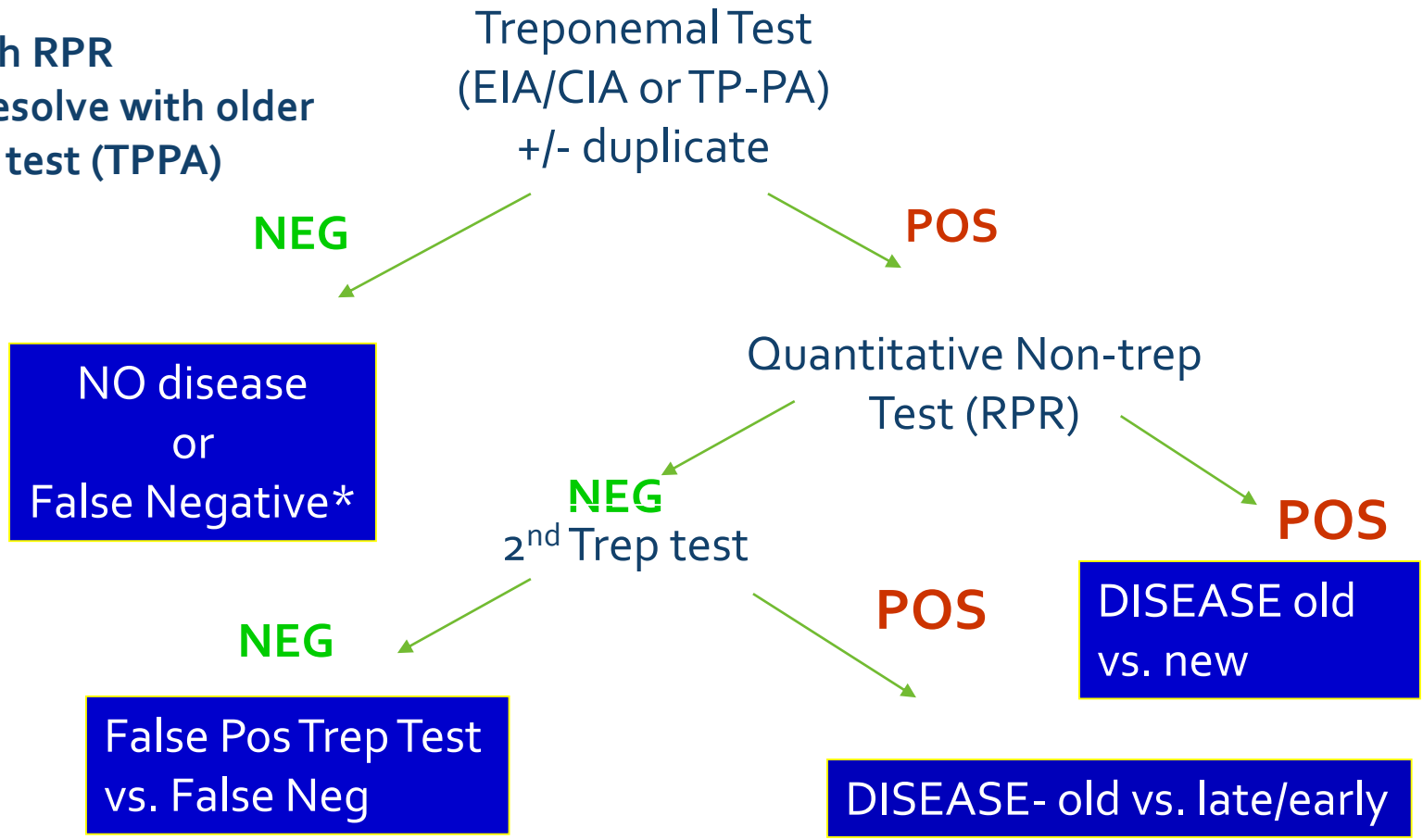
Syphilis Screening Algorithm

- Traditional: 2 serologic tests
  - Screen with nontreponemal test (RPR or VDRL)
  - Confirm with a treponemal specific test (TPPA, MHATP)



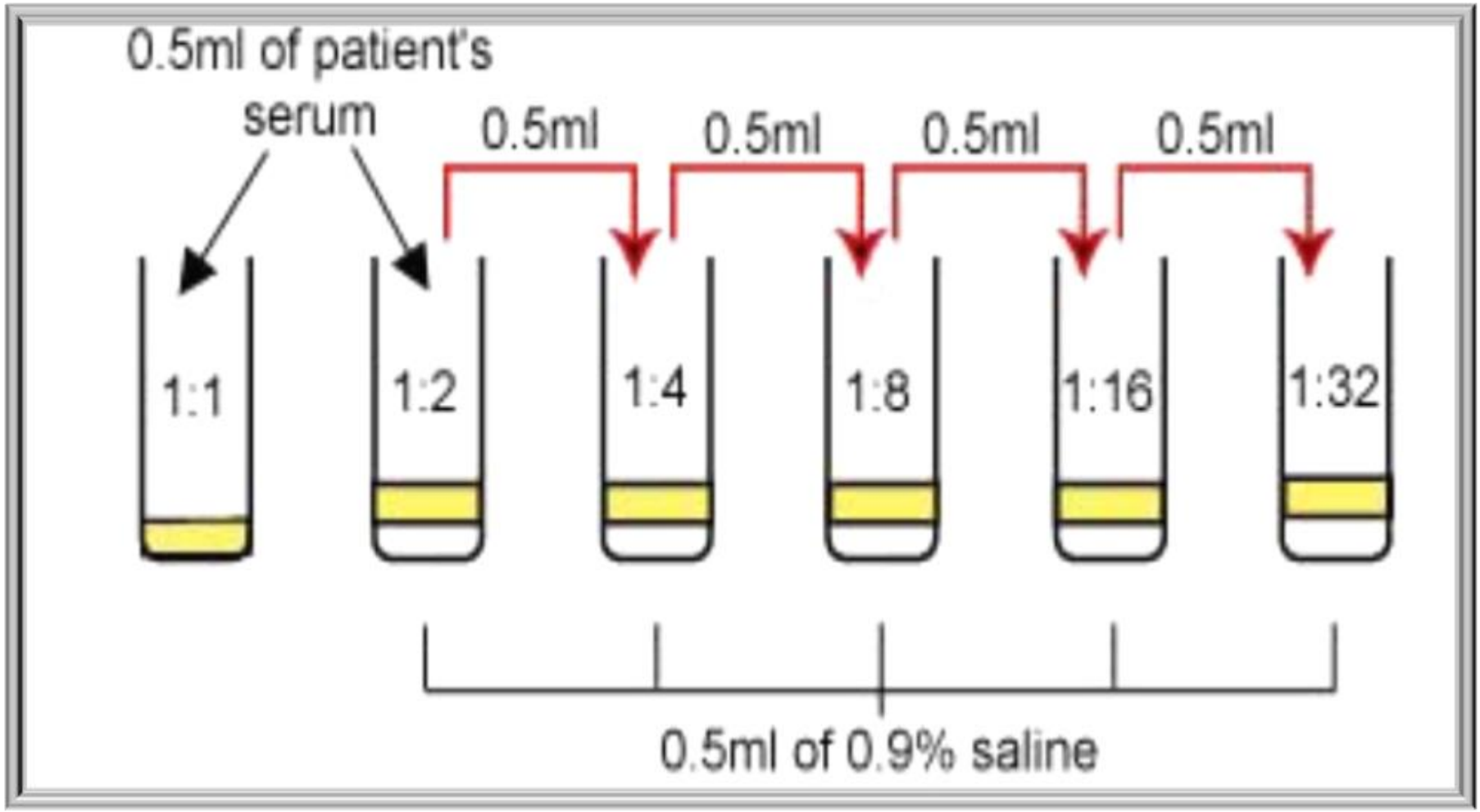
Reverse Sequence Syphilis Screening

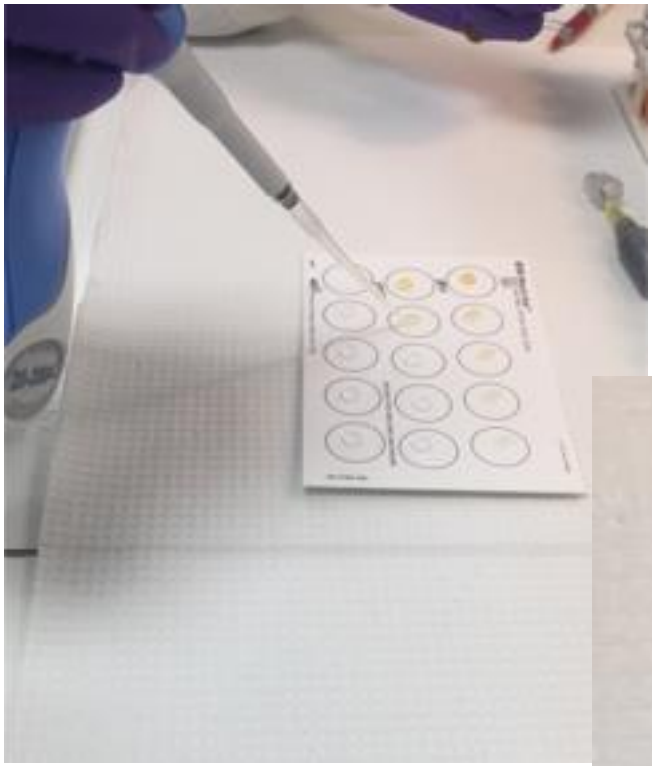
- **Screen with treponemal specific EIA**
- **Confirm with RPR**
- **If conflict: resolve with older treponemal test (TPPA)**

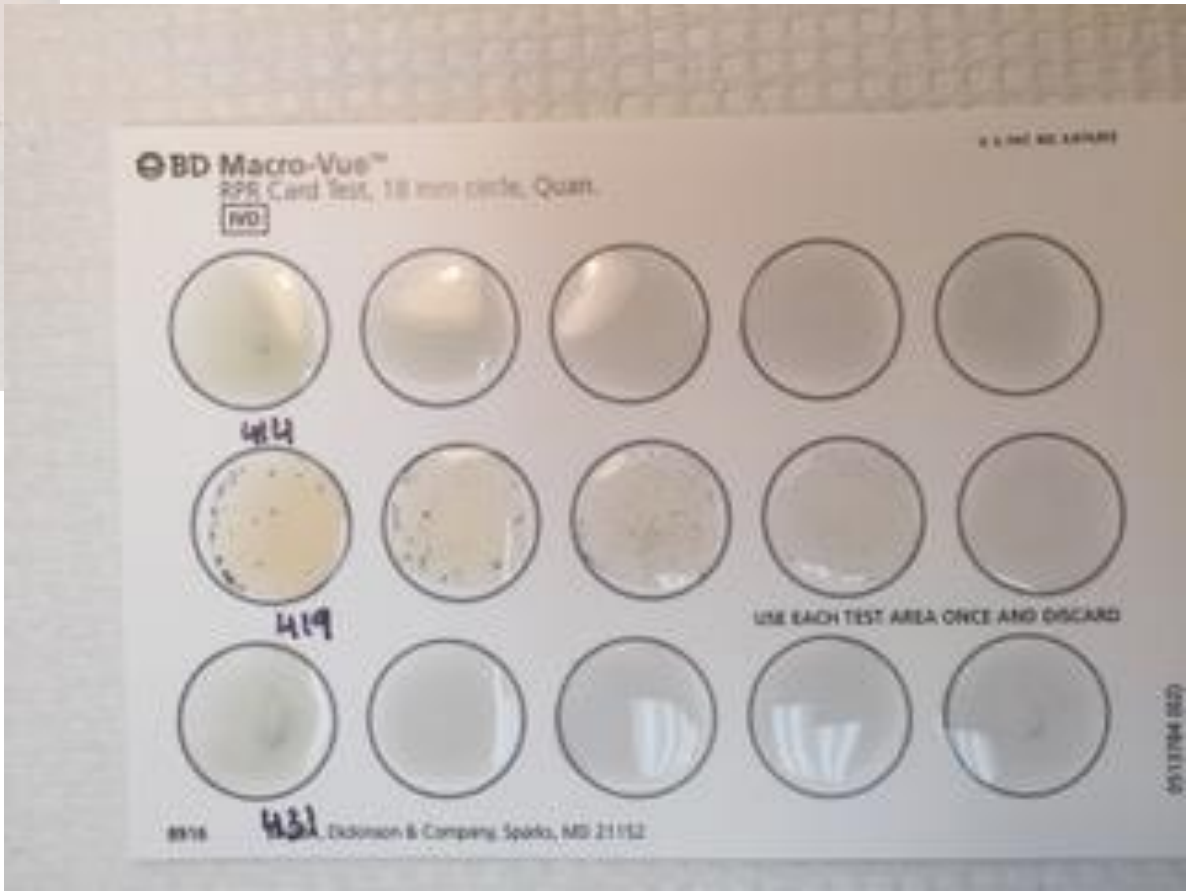


- Do not use EIA in patients with a history of syphilis and in newborns
- False negatives occur in early disease. If high clinical suspicion, repeat tests.

Dilutions of Serum to Obtain RPR Titer







Lab of Paul Swenson, Public Health

Sensitivity of Serological Tests for Syphilis

Test	Primary	Secondary	Tertiary
VDRL	70%	99%	56%
RPR	80%	99%	56%
FTA	85%	100%	98%
TPPA	65%	100%	95%

Case

- 29 yo pregnant woman seen for first pregnancy visit. Her syphilis screening comes back with a reactive RPR (1:2) and a syphilis IgG that is positive.
- She recalls that she was treated for secondary syphilis 2 yeas ago. You obtain records and see that her initial titer was 1:256.
- After treatment, the RPR had fallen to 1:16 at six months, then to 1:2 at 1 year.
- The titer remained at 1:2 two years later.

What is a compelling reason to treat her again?

A) Her syphilis IgG is positive

B) She is pregnant after an episode of syphilis

C) The RPR is still reactive at 2 years post-treatment

D) She doesn't need treatment

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Total Results

Answer

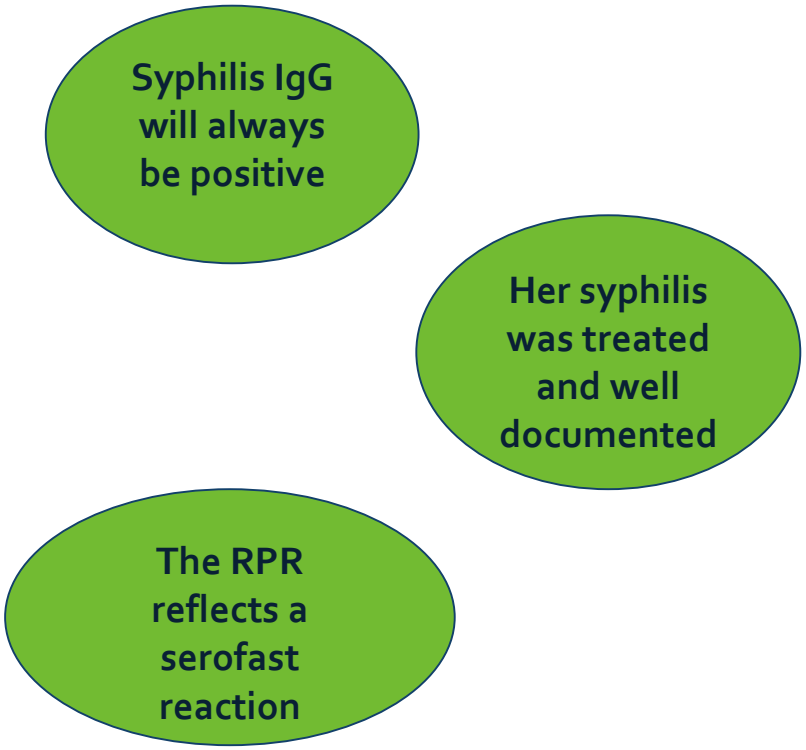
What is a compelling reason to treat her again?

A. Her syphilis IgG is positive

B. She is pregnant after an episode of syphilis

C. The RPR is still reactive at 2 years post-treatment

D. She doesn't need treatment



Serofast state

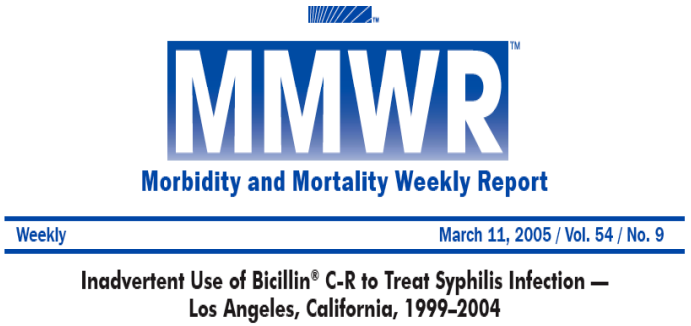
- Serofast reaction = persistent positivity of RPR for years to lifelong at steady state
  - See often in HIV+ patients but also HIV- and pregnancy
  - Does not mean new infection
  - New infection would be diagnosed by an INCREASE in RPR in these patients
  - The syphilis IgG or EIA test will always be positive

Syphilis Treatment

Syphilis Treatment

Primary, Secondary or Early Latent*	2.4 million units Benzathine PCN IM x 1 PCN Allergy- Doxy 100mg bid x 14 days (or tetracycline 500 mg QID x 14 days)
Late Latent or unknown duration	2.4 million units Benzathine PCN IM q week for 3 weeks PCN Allergy- Doxy 100mg bid x 28 days (or tetracycline 500 mg QID x 28 days)

Don't use other PCN formulations!
Don't use azithromycin
PCN ONLY FOR PREGNANT



Jarisch-Herxheimer reaction

- Acute febrile reaction after initiation of antibiotics for the treatment of spirochete infections.
- Death of these bacteria →endotoxins and lipoproteins.
- Fever, malaise, nausea, vomiting, chills, exacerbation of rash.
- Especially in secondary.
- Within 24 hours, resolves in 24 hours.
- The intensity of the reaction indicates the severity of inflammation.
- Self-limiting. Supportive care.

Tell patients they might experience this.

Patient Case

- Your patient, a 47 year old married man, presents with a penile lesion of 4 weeks duration, a generalized rash, sore throat, fever, headache and malaise.
- Your exam reveals palmar and plantar lesions in addition to his reported exanthem, as well as oral mucous patches and generalized lymphadenopathy.

Follow Up Visit

- You treated him with 2.4 MU of Benzathine Penicillin LA for secondary syphilis.
  - He had reported no CNS symptoms at his initial visit .
- His quantitative RPR was 1:512 on the day he came in with his primary chancre and rash. His HIV test was negative.
- His follow up blood test at 3 months post treatment is ***1:64***. Hmmm…. 1:64….

What would you do?

A) Treat again with a single dose of benzathine penicillin 2.4 MU IM

B) Treat with three weekly doses of benzathine penicillin 2.4 MU IM

C) Perform a lumbar puncture

D) Nothing. Repeat testing in 3 months

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Total Results

What did you decide?

- A drop in titer from 1:512 down to 1:64 is an appropriate eight fold* (3 dilution) decline.
- (A titer < four fold (TWO dilutions) is considered evidence of treatment)

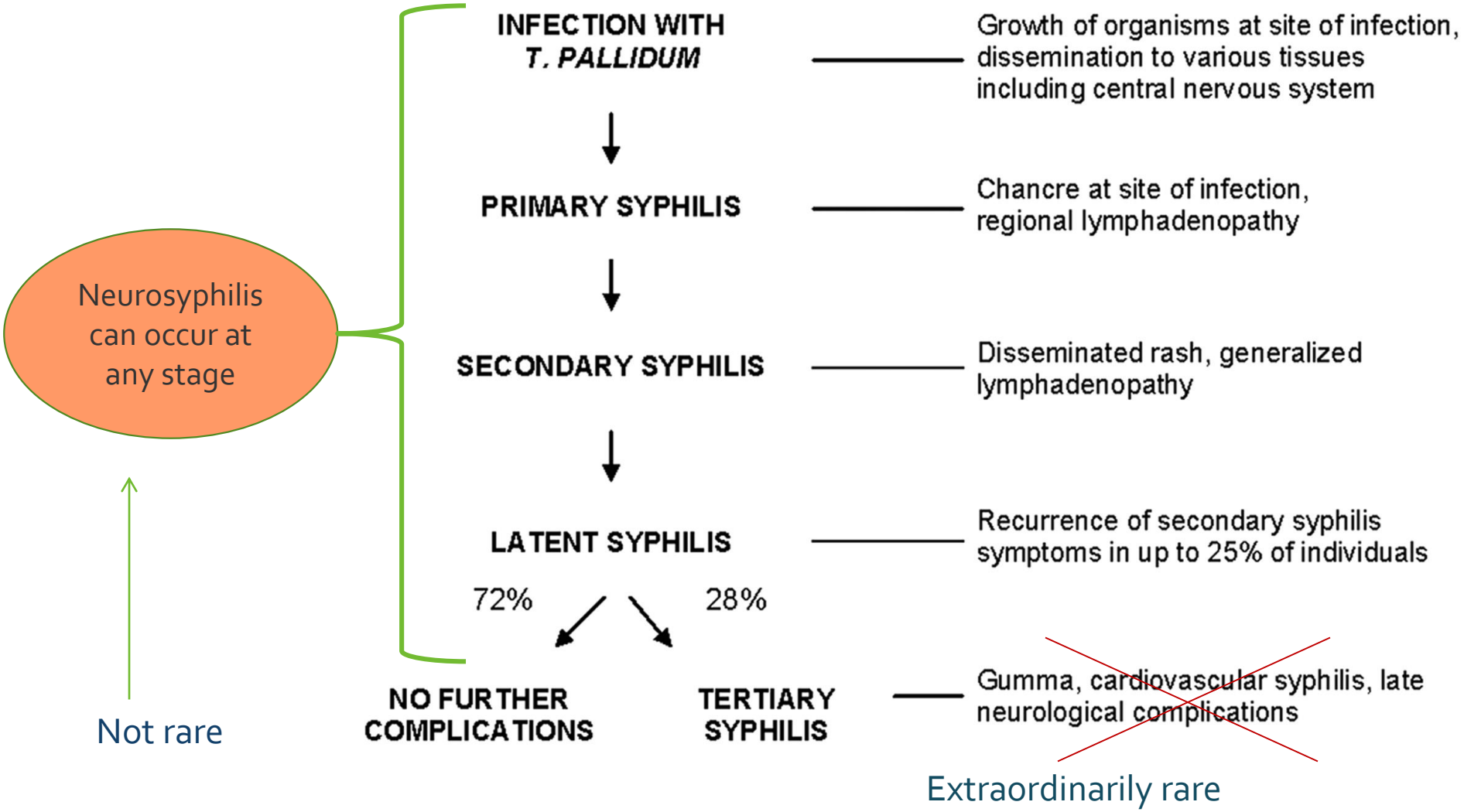
1:512 …→1:256…→1:128…→ 1:64……..1:8…….1:1

Follow up

- HIV negative: retesting at 6 & 12 months for primary and secondary (6, 12 and 24 months for latent disease)
- HIV positive: Evaluated clinically and serologically at 3, 6, 9, 12, and 24 months after therapy.
- Public Health Seattle & King County practice is to test at 3 months (or 1 month), reinfection risk is high
  - Assure continued engagement with care
  - Rescreen for all STIs (HIV!!!)

IMPORTANT: Contacts to syphilis (sex partners)

- Primary, secondary, early latent: treat sex partners as early syphilis x 90 days (even if serology negative)
- **The contact should be treated with first dose of 2.4 million units Benzathine PCN IM without waiting for test results, don't wait for serology. Just treat.
  - Those >90 days → do serology and treat if positive
- Talk to health department re those w late latent syphilis and partners
  - Depends on titer
  - Depends on local epi data


Neurosyphilis can occur at any stage
INFECTION WITH T. PALLIDUM
Growth of organisms at site of infection, dissemination to various tissues including central nervous system
PRIMARY SYPHILIS
Chancre at site of infection, regional lymphadenopathy
SECONDARY SYPHILIS
Disseminated rash, generalized lymphadenopathy
LATENT SYPHILIS
Recurrence of secondary syphilis symptoms in up to 25% of individuals
72%
28%
NO FURTHER COMPLICATIONS
TERTIARY SYPHILIS
Gumma, cardiovascular syphilis, late neurological complications
Not rare
Extraordinarily rare

Neurosyphilis

- Invasion of central nervous system by *T. pallidum*
- Increased protein, WBC in CSF; or reactive CSF VDRL
- Untreated, can progress to meningovascular syphilis (stroke), late neurologic complications
- Ocular syphilis can lead to permanent blindness
- Otosyphilis can lead to permanent hearing loss
- Imperative to screen everyone diagnosed with syphilis

- Patients should have lumbar puncture and treatment for Neurosyphilis

Neurosyphilis – Screening Questions

- Changes in vision? (blurry vision)
- Changes in hearing?
- Tinnitus?
- Headaches?
- Stiff neck?
- Photophobia?
- Discomfort, redness or burning of eyes?
- Other concerning changes: gait changes, sensory loss, cranial nerve abnormalities.

Negative LP does not rule out ocular or otosyphilis

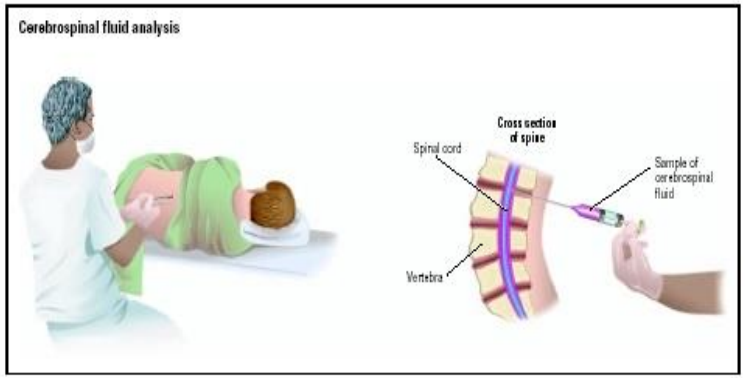
Opthalmologic & Otologic (ENT) referrals

Syphilis Treatment

Primary, Secondary or Early Latent*	2.4 million units Benzathine PCN IM x 1 PCN Allergy- Doxy 100mg bid x 14 days (or tetracycline 500 mg QID x 14 days)
Late Latent or unknown duration	2.4 million units Benzathine PCN IM q week for 3 weeks PCN Allergy- Doxy 100mg bid x 28 days (or tetracycline 500 mg QID x 28 days)
Neurosyphilis (includes oto or ocular)	Aqueous crystalline PCN G 3-4 MU IV q4 or continuous x 10-14d **Or** Procaine PCN 2.4 million units IM + Probenecid 500mg po qid x 10-14 days

CSF in Neurosyphilis

- Pleocytosis
  - >5 for HIV neg WBC/ul
  - Difficult to distinguish from HIV
- Protein concentration
  - > 45 mg/dL
- CSF-VDRL
  - Specific, but not sensitive
- CSF FTA-ABS
  - Sensitive, but not specific



Neurosyphilis

- Patient should be treated promptly with Benzathine penicillin G (Bicillin L-A) - will treat secondary disease
- Risk of loss to follow-up (= transmission potential)
- Don’t delay treatment to arrange LP but try to do LP (important for diagnosis and response to therapy in the future)
- Urgent evaluation by Ophthalmology or ENT if symptoms

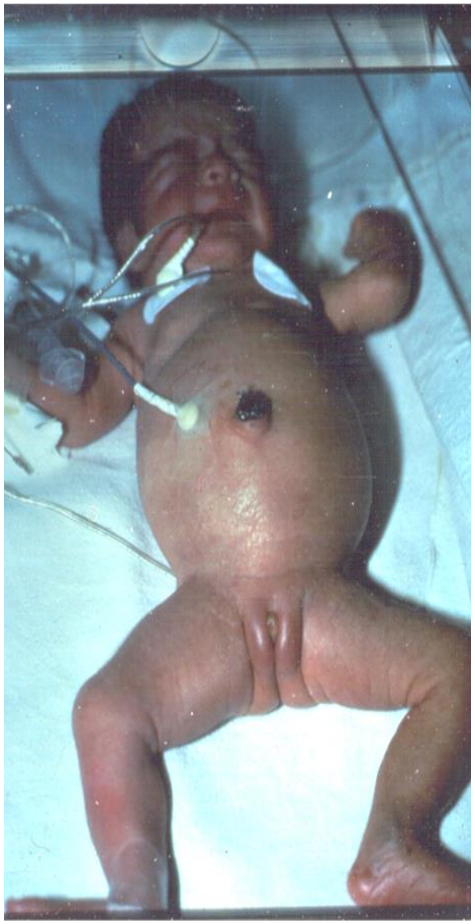
Syphilis & Pregnancy

If positive screen and no history of treatment:

- Penicillin effective for preventing transmission to fetus and treating fetal infection
- Treat with penicillin appropriate for stage of infection
  - Primary, secondary, early latent: benzathine penicillin G 2.4 million units x 1
  - Late latent or unknown duration: benzathine penicillin G 2.4 million units weekly x 3 weeks
  - Assess for neurologic symptoms at any stage of infection
- Reassess titers at 28-32 weeks and delivery
- If mother's titer is reactive at deliver, infant titer must be checked

Congenital Syphilis

- Transplacental infection can occur
  - Any time during gestation
  - Any stage of syphilis
- Results in spontaneous abortion, stillbirth, infant with active or latent syphilis



Screening Recommendations: North and South Dakota

- Pregnant women **three times** throughout pregnancy
  - first prenatal exam, third trimester, delivery.
- Men who have sex with men at least annually, more often if at increased risk
- Persons living with HIV
- Persons at increased risk

Who to Screen: King County

	Risk Criteria	Frequency

MSM	- **Lower risk – Sexually active men outside of mutually monogamous relationships**
	- **Higher risk (based on risk in past year)**
	  - **Bacterial STI**
	  - **Methamphetamine or popper use**
	  - **Condomless anal sex with HIV+/Unknown Status partner**
	  - **>10 sex partners**
	  - **On PrEP**
		Annually
		
		Every 3 months

Pregnant women	- All women - Homeless women, commercial sex, methamphetamine, cocaine or heroin use	- 1st prenatal visit - 1st prenatal visit, 28–32 weeks' gestation & at delivery
Persons with bacterial STIs	- Focus on MSM and gonorrhea	
Homeless persons	- Any sex outside of long-term mutually monogamous relationship	Annually
Methamphetamine users & sex workers	- Any sex outside of long-term mutually monogamous relationship	Every 3 months

Syphilis and HIV/Other STDs

- All patients who have syphilis should be tested for HIV infection.
- Consider screening persons with syphilis for other STDs, based on risk.
- MSM with syphilis and HIV negative→should be counseled to start PrEP (pre-exposure HIV prophylaxis)

STDs predict future HIV risk among MSM

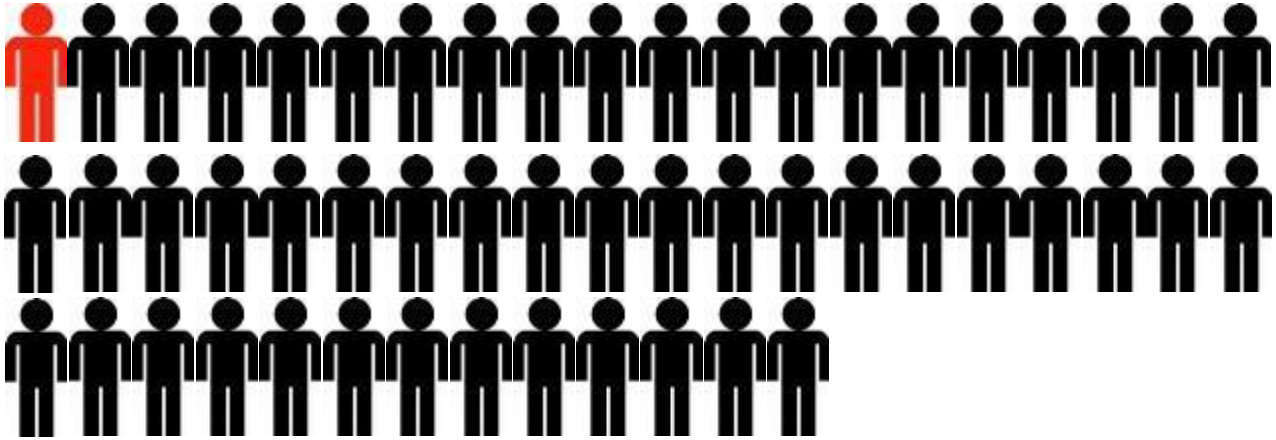
Rectal GC or CT

1 in 15 MSM were diagnosed with HIV within 1 year.*

Primary or secondary Syphilis

1 in 18 MSM were diagnosed with HIV within 1 year.**

No rectal STD or syphilis infection



1 in 53 MSM were diagnosed with HIV within 1 year.*

**STD Clinic Patients, New York City. Pathela, CID 2013:57;*
***Matched STD/HIV Surveillance Data, New York City. Pathela, CID 2015:61*

Slide courtesy of Jessica Frasure Williams, NCSD

Syphilis Statistics: North and South Dakota

49% of cases were symptomatic at time of testing

84% of cases were tested for HIV

16% of cases were HIV positive

Risk factors of those interviewed (67)

- **9%** report injection drug use
- **49%** report sex while high/intoxicated
- **48%** report sex with an anonymous partner

Summary: Approach to Syphilis

Question or Task	Rationale
1) Does the patient have evidence of complicated syphilis?	Determine need for additional work-up
2) What is the syphilis stage?	Determines therapy
3) Test for other STIs (HIV, GC/CT) & pregnancy – Vaccinate for HPV if age ≤26	Define need for other therapy or special follow-up
4) Define HIV treatment or prevention plan	- If HIV positive - Is patient on antiretrovirals and suppressed? - If HIV negative - Recommend PrEP
5) Define follow-up plan	- Assure >2 titer (4 fold) decline over 6-12 months
6) Report to health department	- Helps assure partner treatment, decrease transmission, optimizes care

Syphilis Staging & Treatment

Stage (or complicated)	Criteria for staging	Treatment
Primary	Chancre	2.4 million units Benzathine PCN IM x 1 PCN Allergy - Doxy 100mg bid x 14 days
Secondary	Rash, mucous patches, condyloma lata	
Early Latent* (Early nonprimary nonsecondary)	No symptoms 1 or 2, & ≥1 of the following: 1) Documented 2 titer ↑ in RPR/VDRL in last year 2) Clear history of chancre or rash c/w syphilis in past year 3) Contact to partners with 1, 2 or EL syphilis	
Late Latent or unknown duration	Absence of symptoms 1 or 2 and does not meet criteria for early latent	2.4 million units Benzathine PCN IM q week for 3 weeks PCN Allergy - Doxy 100mg bid x 28 days
Neurosyphilis (includes oto or ocular)		Aqueous PCN 3-4 MU IV q4 or continuous x 10-14d **Or** Procaine PCN 2.4 million units IM + Probenecid 500mg po qid x 10-14 days

STD Resources

University of WA STD Prevention Training Center

- www.uwptc.org

National Network of STD/HIV Prevention Training Centers

- www.nnptc.org

CDC Treatment Guidelines

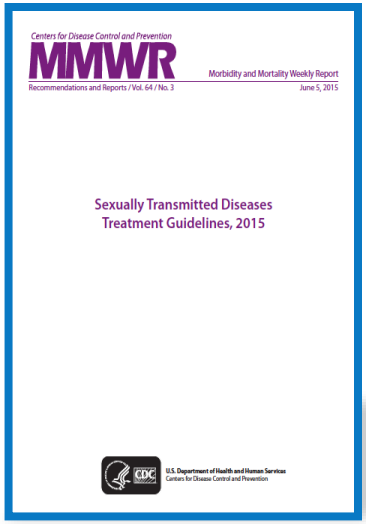
- www.cdc.gov/std/treatment

American Social Health Association (ASHA) booklets, books, handouts, the Helper

- www.ashastd.org
- (800) 230-6039

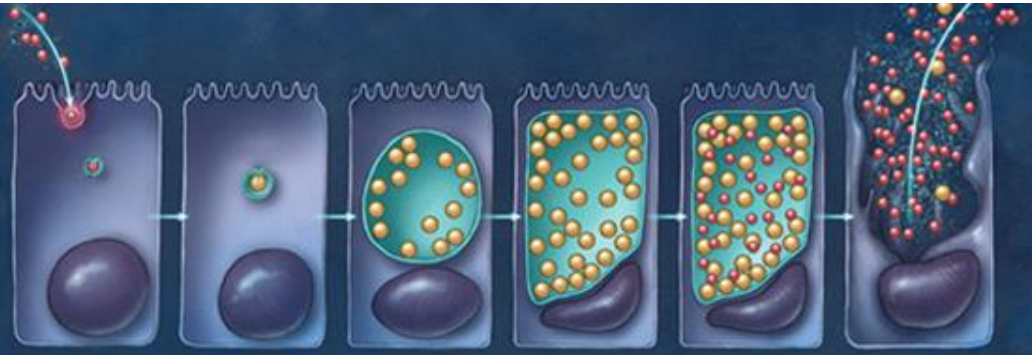
NNPTC National STD Curriculum

- www.std.uw.edu



National STD Curriculum

Funded by a grant from the
Centers for Disease Control and Prevention



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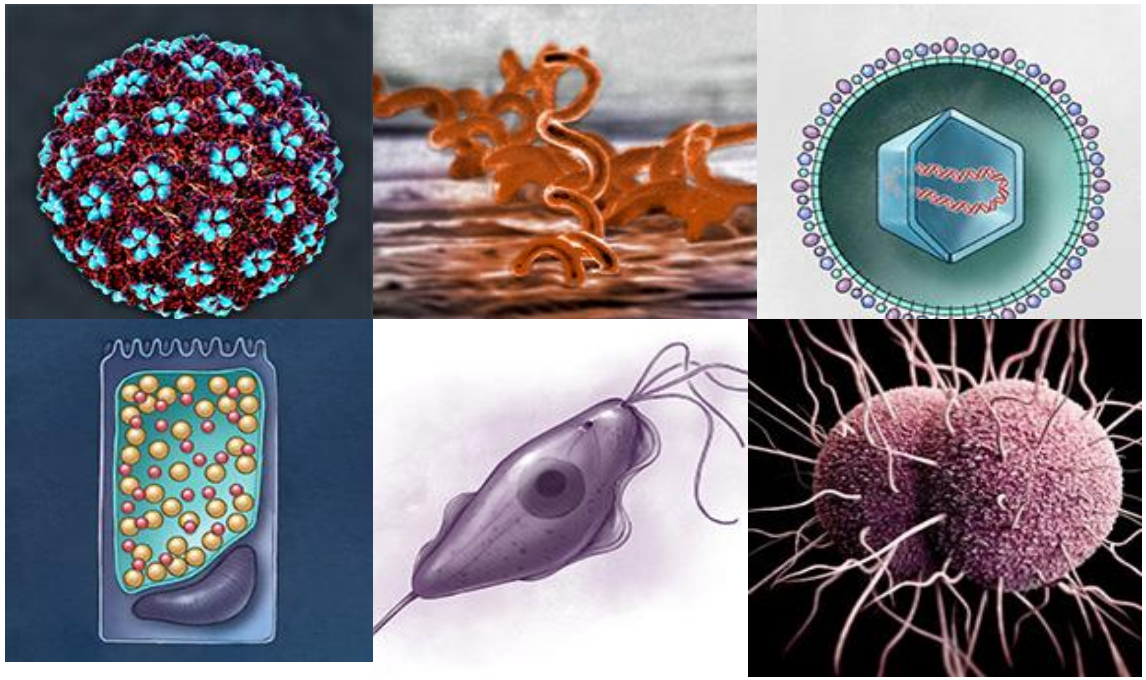

Extra Slides

Causes of Biological False Positive Results (BFP)

- Other infections: HIV, malaria, leprosy, other spirochete infections.
- Older age, autoimmune disorders, cardiovascular disease, pregnancy, recent immunizations.
- False-positive results for the FTA-ABS and TPPA are rare, but are more common for the EIA/CIAs.
- Therefore: confirmed by a second, different, treponemal test.

References:
Golden MR, Marra CM, Holmes KK. Update on syphilis: resurgence of an old problem. JAMA. 2003;290:1510-4.
Nandwani R, Evans DT. Are you sure it's syphilis? A review of false positive serology. International journal of STD and AIDS 1995;6:241–8.